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PERIPHERAL RETINAL HOLES WITHOUT DETACHMENT

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In the following 5 cases, holes in the periphery of the retina were observed without detachment. I am purposely leaving out of this consideration cases of macular holes, as these have a different causation and a different course. The importance of retinal holes in the causation of retinal detachment is generally accepted; therefore I may be justified in reporting these cases to illustrate that retinal holes may occur without detachment.

CASE 1.—J. R. M., a woman aged 61, complained on Aug. 26, 1908 that the sight in the left eye had become clouded ten days previously. There were present fine opacities of the vitreous and some edema of the retina in the nasal periphery, but no detachment. There was an irregular hole of about disk size just below the horizontal meridian in the nasal periphery in which the choroidal vessels could be distinctly observed. At the margin the retina appeared brownish, possibly because of choroidal pigmentation. On Jan. 9, 1909, four months later, the edema and the hole in the retina were unchanged. The patient was then lost sight of.

CASE 2.—G. G., a woman aged 53, had an intracapsular extraction done on the right eye on April 12, 1928. There were no complications, and normal vision was obtained. On March 28, 1935 the patient complained that a shadow had been present before the right eye for one week. Vision with glasses was 20/20—. In the upper and outer periphery the retina was grayish, and a definite hole was present, but no detachment. This hole, about ⅛ disk diameter, was round, with grayish margins and a lid hanging down like a flap. It was directly next to one of the larger vessels. There was no detachment. The patient was observed at regular intervals and when she was last seen, on May 19, 1942, seven years after the onset of the difficulty, the corrected vision in the right eye was 20/20, there had been no change in the retina or in the hole and there was no ophthalmoscopic evidence of choroidal changes.

CASE 3.—M. J. F., a woman aged 60, complained on Dec. 2, 1937 of a sudden obscuration of the right eye; when she was examined the following day the vision with a correction of −6.00 D. sph. ⌒ −4.50 D. cyl., axis 180 was 20/200. There was a field defect in the lower and inner quadrant. There was a considerable number of opacities from blood in the vitreous. On December 6 the vision had improved, the field was less contracted and the fundus was clearer. A semicircular hole, about ¼ disk diameter, with a wrinkled margin above, could be distinctly seen in the retina at 11 o'clock. The patient was treated with rest, subconjunctival injections of saline solution and administration of vitamin C. When she was seen on Jan. 8, 1942 the vision with glasses was 20/30. There were a few opacities of the vitreous. The retina was unchanged. In the upper and outer periphery of the retina there was the same semicircular hole with a flap at the upper margin, and a little beyond it was a second and much smaller linear hole. The entire area was outlined by a crescentic chorioretinal pigmented line. The condition was unchanged when the patient was last seen, on Feb. 15, 1943.

CASE 4.—R. W. B., a man aged 67, complained on June 25, 1942 that the sight of the left eye had been blurred for four days. The vision was 20/50. There were diffuse opacities of the vitreous (blood), and up and out at 2 o'clock there was a definite round hole of about ¼ disk diameter, with a separated flap like a lid suspended a little anteriorly in the vitreous. There was no detachment. No change had occurred when the patient died three months later from heart disease.

CASE 5.—A. J., a woman aged 40, was seen on July 6, 1929 with a history of failure of vision of the left eye for three days. The vision with a correction of −5.50 D. sph. ⌒ 1.00 D. cyl.,

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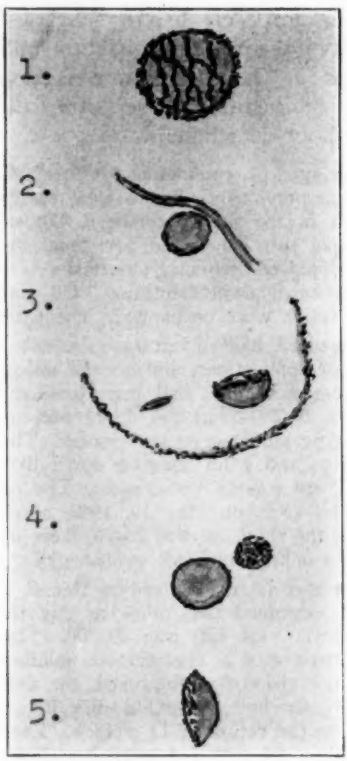
axis 60 was 20/30. There were recent opacities of the vitreous (blood), and at about 1 o'clock there was a vertical oval hole with a grayish opacity at the nasal margin like a wrinkled flap. There was no detachment. The right eye was blind from an old detachment. On Oct. 10, 1929, the vision of the left eye with glasses was 20/30. The vitreous was clear. The hole in the retina could be easily seen, and one margin protruded into the vitreous. There were no choroidal changes. On Jan. 9, 1930, six months after the onset of the trouble, the vision became worse; a detachment was definitely present, surrounding the area of the retinal hole in the upper and outer quadrant. The patient was then operated on.

To recapitulate, in case 1 there was a round hole of about 1 disk diameter in the nasal periphery of the retina. The margin of the hole was faintly pigmented, suggesting a chorioretinal adhesion. There was no detachment. The patient was lost sight of after four months. In case 2 a small hole developed in an aphakic eye near a blood vessel in the upper and outer periphery of the



Peripheral retinal holes without detachment (cases 1, 2, 3, 4 and 5).

retina. The margins of the hole were gray and a lidlike flap hung down from above. There was no detachment. This case was observed for seven years. There was no change. In case 3 two retinal holes were present in the upper and temporal periphery of the retina. This area became shut off by a line of choroidal pigmentation. There was no detachment. The case was followed for five years. In case 4 there was a hole in the upper and outer periphery with a stationary operculum but no detachment. This operculum can be explained only by the presence of a detachment of the vitreous. No change occurred; the patient died three months later. In case 5 there was an oval hole in the upper and outer periphery with a wrinkled flap attached to the nasal margin. There was no detachment. Six months later a detachment developed in this part of the fundus. The other eye was blind from an old detachment.

In 3 of these cases the lesion began with a hemorrhage into the vitreous. It is important to remember that hemorrhages into the vitreous in older persons may result from a tear in the retina and are not necessarily due to arteriosclerosis, a fact to which Vogt [1] has drawn attention.

A study of the literature reveals that holes without detachment are not unusual. I have found the following references.

Gonin [2] stated the belief that certain tears, especially perforations of atrophic origin or more unusually disinsertions, may not always or immediately be followed by a detachment in the surrounding retina.

Arruga [3] published drawings illustrating 2 cases in which the tear was surrounded by pigmentation, which indicate a healed inflammatory process and a circular hole with a freely suspended operculum.

Lindner [4] stated the belief that spontaneous retinal tears without detachment are explained by an adhesion between the retina and the choroid which prevents the development of a retinal detachment.

Vogt [5] reported 3 cases of traumatic tears at the ora in which the symptoms came on late, and 2 of spontaneous round holes with freely suspended operculums, without detachment.

Sabbatini [6] reported 5 cases of retinal holes without detachment. About the holes chorioretinitis was present. The margins of the holes were not everted, and there were no signs of traction of the vitreous. In 1 case the hole was seen to heal. The edges lost their grayness, and new choroidal areas developed. The usual subjective symptoms were absent.

Jeandelize and Baudot [7] on casual examination of the eyegrounds of patients undergoing refraction discovered 3 retinal tears without detachment. One was at the ora. One was in the periphery and was round, with pigment along the macular border. A third was oval and larger than the disk, with exposed choroidal vessels and some pigment along the border.

Burch [8] reported on an extensive tear in the retina which was under observation for twelve weeks without the development of a retinal detachment. The tear was 2 mm. in breadth and extended along the superior temporal vessels 3 disk diameters from the disk to the periphery.

Genet [9] reported 1 case of a round hole in the retina with choroidal changes after hemorrhage into the vitreous. He said that a hole alone is not sufficient to cause detachment. There must be in addition histologic lesions in the retina; in other words, the retina cannot be sound. Amsler in the discussion said that there must always be changes in the choroid, retina and vitreous to produce a retinal hole.

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1. Vogt, A.: Photographie einer Bienenwabenmakula bei Retinitis pigmentosa juvenilis, Klin. Monatsbl. f. Augenh. **102**:519, 1939.

2. Gonin, J.: Le décollement de la rétine, Paris, Payot & Cie, 1934, p. 77.

3. Arruga, H.: Detachment of the Retina, translated by R. Castroviejo, New York, B. Westermann, 1936, p. 76.

4. Lindner, K.: Zur Klinik des Glaskörpers, Arch. f. Ophth. **137**:183, 1937.

5. Vogt, A.: Die operative Therapie und die Pathogenese der Netzhautablösung, Stuttgart, Ferdinand Enke, 1936, p. 123.

6. Sabbatini: Rotture retiniche senza distacco, Atti Cong. Soc. oftal. ital., 1935, p. 763.

7. Jeandelize, P., and Baudot, R.: Aspects de déchirure rétinienne sans décollement appréciable, Ann. d'ocul. **170**:515, 1933.

8. Burch, F. E.: Extensive Retinal Tear, Am. J. Ophth. **21**:669, 1938.

9. Genet, L.: Déchirures rétiniennes sans décollement, Bull. et mém. Soc. franç. d'opht. **49**:262, 1936.

Guillot [10] regularly explored the retinal periphery in all myopes who complained of recent opacities and found several holes without detachment or with limited detachment.

Nico Trantas [11] wrote that A. Trantas insisted on the existence of retinal holes without detachment in myopic eyes. His 5 cases were insufficiently reported. Mention was made of the importance of examining the periphery of the eyeground with the aid of digital pressure in cases of sudden opacities of the vitreous.

Arruga [12] said that if a detachment does not follow a hole an adhesion of the retina to the choroid must be present to prevent the escape of fluid underneath the retina.

Hanssen,[13] in a study of the development of detachment in myopic eyes, examined histologically 37 myopic eyeballs without detachment. In 26 there were partial thinning of the retina, cystoid degeneration, slight tears in the inner retinal layers and direct holes. Of the eyes with the changes situated in the anterior part of the eyeball, slight tears were present in 4 and holes in 3, while in the 6 eyes with changes at the equator there were 2 holes. Hanssen regarded the retinal hole as the most important predisposing cause of detachment. He stated the belief, however, that to produce detachment degenerative changes in the vitreous and reduced intraocular pressure must also be present.

These authors explained retinal holes without detachment by the formation of chorioretinal adhesions. While it is clear that an adhesion between the retina and choroid can prevent detachment, choroidal changes were not apparent on ophthalmoscopic examination in 3 of my cases and another explanation should be considered. It may not be out of place to see how these cases fit into the present interpretation of the formation of so-called idiopathic retinal detachment.

Retinal holes without detachment belong to Gonin's second group: round, relatively small holes situated in the equatorial zone or just anterior to it and usually in the lateral or inferior part in a retina which is only slightly raised. This type is due to cystoid degeneration or atrophy of the retina resulting from nutritional disturbances, together with disease of the choroid and deep changes in the vitreous (Amsler and others [14]).

In addition, an adhesion of the vitreous to the retina is believed to be present. Adhesions between the hyaloid membrane and the internal limiting membrane occur in every healthy eye, especially at the base of the vitreous. The cause for this adhesion is not known; it is assumed to result from pathologic processes such as degenerative or inflammatory changes in the retina, as had been suggested by histologic examination. In a case of Sourdille's,[15] adhesion of the operculum to the vitreous was present, and the torn-out piece of retina showed inflammatory changes which were believed to explain the adhesion of the vitreous. Vogt [5] came out definitely with the view that degenerative changes must be present in the

10. Guillot, P.: Des déchirures rétiniennes sans décollement, Bull. et mém. Soc. franç. d'opht. **48**:317, 1935.

11. Trantas, N.: Sur l'opération du décollement de la rétine par diathermo-coagulation d'après la méthode de Weve, Bull. et mém. Soc. franç. d'opht. **50**:234, 1937.

12. Arruga, H.: Etiology and Pathogenesis of Retinal Detachment, Arch. oftal. hispano-am. **33**:312, 1933.

13. Hanssen, R.: Zur Entstehung der Netzhautablösung, Klin. Monatsbl. f. Augenh. **74**: 778, 1925; **75**:463, 1926.

14. Amsler, M., and others, in Bailliart, P.; Coutela, C.; Redslob, E., and Velter, E.: Traité d'ophtalmologie, Paris, Masson & Cie, 1939, vol. 5, p. 525.

15. Sourdille, G.: Étude histologique de 2 cas recents de décollement de la rétine, Cong. Soc. franç. d'opht., 1932, p. 236.

retina before a rupture can take place. These changes consist in cystoid degeneration and nutritional disturbances in the retina without involvement of the vitreous. Leber [16] stated the belief, and his views were accepted by Gonin and Lindner, that rupture of the retina occurs at the place where adhesion between the vitreous and the retina has taken place.

Changes in the vitreous are particularly important in the pathogenesis of retinal detachment. It is generally accepted that the vitreous undergoes liquefaction and contraction and that a detachment of the vitreous ensues. Lister [17] stated the belief that detachment of the vitreous is common and is due to actual contraction of the vitreous or its liquefaction. This author suggested that traction of an adhesion between the retina and a contracting vitreous is sufficient to cause a rent. This tearing could be more easily produced on sudden rotation of the eye, especially if the retina was weakened by cystic degeneration. Lindner [18] favored the role of the vitreous in the development of a detachment and said that a posterior detachment of the vitreous is essential. Especially important is the partial fluidification of the vitreous; this makes traction of the vitreous uneven and leads to rupture of the vitreous or retina with escape of fluid from the vitreous. Lindner [19] has examined histologically many eyes with retinal detachment and found that the detached vitreous was adherent to the peripheral margin of the retinal tear and that the subvitreous space and subretinal space were in communication. Sallmann and Rieger [20] proved clinically the presence of a detachment of the vitreous in nearly all cases of retinal detachment. The clinical examination was made possible by the use of Lindner's angular microscope and a contact glass. Unfortunately only a part of the fundus about the posterior pole can be examined by this method and a clear vitreous is essential. Sallmann [21] has demonstrated the frequent presence of a detachment of the vitreous in freshly enucleated eyes. Böck [22] was fortunate enough to make a satisfactory examination of the vitreous in 2 cases of retinal detachment before and after operation. In these cases an adhesion between the peripheral margin of the hole and the vitreous was observed and the adhesion persisted after the successful operation. Vogt accepted the statement that detachment of the vitreous is frequently present in cases of detachment of the retina but claimed that it occurs even more frequently without such detachment in senile and myopic eyes and in eyes with senile and presenile destruction of the framework of the vitreous. He had never observed a case of detachment of the vitreous in which a detachment of the retina subsequently appeared.

Best [23] drew attention to the clinical fact that localization of the tear is three times as frequent in the upper part as elsewhere, and the same proportion holds true for the site of detachment. Hence it is clear that gravity must play a definite role and increase the pull of the vitreous.

16. Leber, T., in Graefe, A., and Saemisch, E. T.: Handbuch der gesamten Augenheilkunde, Berlin, Julius Springer, 1916, vol. 7.

17. Lister, W.: Detachment of the Vitreous, Tr. Internat. Cong. Ophth., 1922, p. 63.

18. Lindner, K.: Zur Klinik des Glaskörpers, Arch. f. Ophth. **137**:158, 1937.

19. Lindner, K.: Zur Klinik des Glaskörpers, Arch. f. Ophth. **137**:170, 1937.

20. Sallmann, L., and Rieger, H.: Ueber hintere Glaskörperabhebung bei Ablatio retinae, Arch. f. Ophth. **133**:75, 1934.

21. Sallmann, L.: Zur Anatomie der hinteren Glaskörperabhebung, Arch. f. Ophth. **135**: 593, 1936.

22. Böck, J.: Ueber den klinischen Nachweis der Anheftung des Glaskörpes am Rissrand bei Netzhautabhebung, Arch. f. Ophth. **140**:468, 1939.

23. Best, F.: Zur Pathogenese der Netzhautablösung, Ber. ü. d. Versamml. d. ophth. Gesellsch. **33**:186, 1906.

The movement of the vitreous is another important factor in the development of a detachment. Best [24] has demonstrated that in every movement of the eyeball the vitreous undergoes movement, exerting a pull on the peripheral parts where the hyaloid membrane adjoins the internal limiting membrane of the retina. Lindner [25] has particularly emphasized the importance of ocular movements, and his interesting experiments have confirmed Lister's views that the rotating and torsional movements are the more powerful. Vogt [26] had also accepted the role of movement of the vitreous in the development of a detachment and mentioned the enormous whirling of the framework in the myopic and senile vitreous when this is examined with the slit lamp microscope. According to Lindner the vitreous pulls on the retina during rotating and whirling movements of the eyeball and causes a rupture just at the margin of the attachment of the vitreous.

The nondevelopment of a retinal detachment may be due to the absence of any one of these factors.

It seems reasonable to assume that in the case of certain types of holes the changes in the retina are a sufficient explanation and that in the case of retinal holes without detachment the changes in the vitreous are not developed to the extent necessary to cause detachment. If one leaves aside the question of adhesion and traction of the vitreous, the fact that a detachment did not occur in the cases described in this article must mean that there was no access to the subvitreous fluid or that if the vitreous was not detached there was no tear in the hyaloid membrane to permit escape of fluid from the vitreous.

When detachment of the vitreous is absent, changes in the texture of the vitreous were assumed by Vogt, such as partial liquefication with formed vitreous elements, which on whirling movements of the eye traumatize a weakened retina at the site of an adhesion.

As for treatment, the patient naturally should be kept under observation and examined for the presence of a detachment of the vitreous. Amsler [27] expressed the opinion that a retinal tear should be operated on even if no detachment has occurred. I agree with Vogt that an operation is not necessary before the detachment develops. At the same time a history of detachment in the other eye is ominous, as in case 5 of my series, and suggests that similar changes probably will occur in the recently affected eye. The operation before the retina becomes detached should be a simple one.

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24. Best, F.: Der Glaskörper bei Augenbewegungen, Klin. Monatsbl. f. Augenh. **42**:538, 1904.

25. Lindner, K.: Prevention of Spontaneous Retinal Detachment, Arch. Ophth. **11**:148 (Feb.) 1934.

26. Vogt, A.: Histologischer Befund eines weiteren Falles von relativ frischer spontaner (senil-myoper) Netzhautablösung, Monatsbl. f. Augenh. **98**:735, 1937.

27. Amsler, M.: Muss ein Retinariss operiert werden, auch wenn eine Ablatio nicht eingetreten ist? Klin. Monatsbl. f. Augenh. **101**:920, 1938.

CARBAMINOYLCHOLINE CHLORIDE IN PETROLATUM

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Carbaminoylcholine chloride is a synthetic drug introduced in 1932 as a long-acting substitute for acetylcholine. The drug produces miosis and cyclotonia and decreases intraocular pressure; consequently, it is used as an agent in the treatment of glaucoma. Carbaminoylcholine chloride is poorly absorbed from the conjunctival sac when instilled in simple aqueous solutions; however, O'Brien and Swan [1] found that when precautions were taken to insure absorption, carbaminoylcholine chloride had a more intense and prolonged hypotensive effect on glaucomatous eyes than had corresponding doses of pilocarpine salts. They observed that the addition of a surface tension–reducing agent, zephiran chloride, facilitated penetration of carbaminoylcholine chloride from aqueous solutions into the normal cornea. However, other precautions are necessary to insure absorption. The solution of the drug must be administered so that it covers the cornea, and the lids must be kept closed to maintain good contact between the cornea and the solution for at least several minutes. Massage of the cornea through the lids further enhances absorption. Recent investigations have suggested a simpler and more effective method of administration of the drug.

Swan and White [2] demonstrated that the physical properties of the drug and the vehicle profoundly affect the rate of penetration of a given drug into the cornea. The relative affinities of the drug for the cornea and for the vehicle are particularly important. Most substances of low surface activity, high affinity for water and low affinity for lipids enter the normal cornea slowly when administered in simple aqueous solutions. When these substances are administered as a suspension in pure olive oil or petrolatum, penetration is rapid. Carbaminoylcholine chloride has the physical properties of this class of substances; consequently, it should be most effectively administered as a suspension in pure oil.

PRESENT STUDY

Experiments were made on the eyes of albino rabbits. Effectiveness of absorption of carbaminoylcholine chloride was judged by the onset, intensity and duration of miosis produced by contact of a given concentration of the drug with the cornea for specific periods. An ointment base of pure petrolatum [3] was observed to be a considerably more effective vehicle than zephiran solution (1:3,500) or zephiran jelly (1:2,000) and many times more effective than distilled water. The addition of hydrous wool fat to the petrolatum resulted in decreased absorption, probably because the hydrous wool fat contained sufficient water to retain the hydrophilic

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1. O'Brien, C. S., and Swan, K. C.: Carbaminoylcholine Chloride in the Treatment of Glaucoma Simplex, Arch. Ophth. **27**:253 (Feb.) 1942.

2. Swan, K. C., and White, N. G.: Factors Affecting Penetration of Drugs into the Cornea, Am. J. Ophth. **25**:1043, 1942.

3. The consistency of the ointment was adjusted by mixing liquid petrolatum U. S. P. and white petrolatum. A stable and even suspension was readily obtained, as carbaminoylcholine chloride was available in sealed ampules as a fine, dry powder.

carbaminoylcholine in the ointment and to prevent its transmission into the cornea. When the corneal epithelium was removed or damaged, differences in the effectiveness of the various vehicles were reduced greatly.

In clinical experiments the ointment was prescribed in small ophthalmic tubes with pointed tips to facilitate self administration and accurate dosage. Patients were instructed to look into a mirror and squeeze out a quarter of an inch (0.6 cm.) of ointment (0.05 cc.) onto the conjunctival side of the everted lower lid and then to look down in order to bring the ointment into contact with the cornea. They were advised that temporary blurring of vision occurs as the ointment spreads on the cornea and that this blurring indicates that the ointment is properly applied.

Clinical experiments were made on a group of 15 eyes (9 patients) with chronic noncongestive glaucoma. Pilocarpine administered three to four times daily was ineffective in controlling the tension or in preventing visual loss. Carbaminoylcholine chloride (1.5 per cent in 0.03 per cent solution of zephiran chloride) administered three to four times daily was effective in maintaining the tension below 30 mm. mercury (Schiøtz) and in preventing loss in the visual fields in 11 of the 15 eyes during periods of five months up to three years. However, carbaminoylcholine chloride (1.5 per cent) in petrolatum administered only twice daily was equally effective in controlling the tension in these 11 eyes. In 2 eyes the tension was not consistently controlled by carbaminoylcholine chloride in solution of zephiran chloride when the drug was administered at home three to four times daily, but administration of the ointment twice daily at home was successful. In the fourteenth and fifteenth eyes, carbaminoylcholine chloride in any vehicle did not effectively control the tension, although miosis (2.5 mm. pupil) and spasm of accommodation (0.75 to 2.75 D.) were maintained more consistently with the ointment than with zephiran solution or zephiran jelly.

The clinical studies indicated that a suspension of carbaminoylcholine chloride in pure petrolatum was more effective than the same percentage of carbaminoylcholine chloride in solution of zephiran chloride, particularly when applications of the drug were made by the patient or by his family. Only 3 of the 9 patients considered that administration of the ointment was more difficult than that of the carbaminoylcholine chloride–zephiran solution. All found the ointment to be more economical, as less frequent administrations were required.

SUMMARY

Carbaminoylcholine chloride has a high affinity for water and a low affinity for lipids. Like other substances with these properties, it penetrates the normal human and rabbit cornea more readily when administered as a suspension in a pure petrolatum base than when given in simple aqueous solutions, in a solution zephiran chloride or in ointment bases containing hydrous wool fat. In the treatment of chronic noncongestive glaucoma, administration of carbaminoylcholine chloride in petrolatum is more effective and economical than other methods of administration of the drug.

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GUIDES IN THE OPERATIVE (COSMETIC) TREATMENT OF NONACCOMMODATIVE CONCOMITANT SQUINT IN ADULTS

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The question as to how one can be guided in determining the amount of operative correction and the selection of the proper muscles for operation for relief of squint has been raised many times. Many diverse answers have been given. The amount of correction described as obtainable with a measured amount of shortening or lengthening of a specified muscle has varied greatly. So many variable factors were found in the reports that it was felt that a series of operations for squint in which the variables were minimized would give valuable information. Such a series of operations were performed at the Barnes General Hospital during a period of approximately one year.

MATERIAL AND METHOD

The group consisted of 65 operations on the internal and external rectus muscles of male Army personnel, ranging in age from 20 to 49 years. All operations were performed by the same surgeon. No patients with pronounced anomalous retinal correspondence, strabismus fixus, accommodative squint or a marked vertical component were included in this series. In addition, a considerable number of men with alternating divergent squint, especially those of the divergence excess type, were excluded because the preoperative deviation under cover varied considerably at different examinations. After operation the angle did not vary, but at times the postoperative deviation was greater than the deviation before operation. Patients of this type should have a period of monocular occlusion before examination. In addition, the cover should not be alternated as rapidly in examination of these patients as in tests on persons with other types of squint.

The angle of squint was measured by the cover test, for both 20 feet (6 meters) and 33 cm., loose prisms being used for all patients with normal fixation in each eye. With the patients whose fixation was eccentric or poor, the perimeter was used for measurement.

Each patient was tested for the possible development of postoperative diplopia due to the presence of pronounced anomalous retinal correspondence before operation by placing the full prismatic correction which was necessary to stop movement of the eye under cover before the uncovered eyes and determining whether diplopia was present. If an annoying diplopia appeared, the probability of such a postoperative condition was explained to the patient. Usually operation was not done under such circumstances.

Only two types of operative procedure, resection and recession, were included in this series, not only because this limitation in the range of operations was desirable but because these two procedures have been adequate in correcting safely practically all types of horizontal strabismus. In some patients with divergent squint, complete tenotomy of one or both external rectus muscles was necessary to obtain parallelism. These patients were not included, however.

The resection operation used was the Lancaster procedure, modified as follows: The conjunctiva was incised vertically in a separate layer just in front of the insertion of the muscle. Tenon's capsule was then incised vertically. The cut edge of the conjunctiva and capsule on the side away from the limbus was lifted so as to expose the muscle and the capsular reflections. The latter were cut as far back as the resection was expected to extend. A Prince forceps was introduced and clamped on the muscle just in front of the measured amount of muscle to be resected. The tendon was then severed just behind its attachment to the sclera. Two double-armed 0000 mild chromic sutures were passed through the stump from within outward. Each was then passed through the muscle just behind the Prince forceps, from within outward, and then tied over the muscle. The forceps was removed

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and the excess muscle resected. Tenon's capsule and the conjunctiva were closed with a continuous silk suture.

The recession operation used in this series was the Jameson procedure, modified as follows: The conjunctiva was incised vertically in a separate layer just in front of the insertion of the muscle. Tenon's capsule was similarly incised, and the cut edge of the capsule and conjunctiva on the side away from the limbus was lifted so as to expose the muscle and the capsular reflections. The latter were cut, and a strabismus hook was inserted under the muscle at its attachment. A single-armed 0000 chromic catgut suture on an atraumatic needle was whipstitched into each side of the tendon just behind its attachment. The hook was removed and the tendon attachment severed, the sutures being used for traction. The muscle was then retracted, and the needle of each suture was passed through the superficial layers of the sclera. Each suture was then tied separately. The conjunctiva and Tenon's capsule were closed with a continuous silk suture.

In all the operations local anesthesia was used, both by instillation and by injection. A 5 per cent solution of cocaine hydrochloride was used by instillation in six doses of 1 drop each at two minute intervals. One-half cubic centimeter of a 2 per cent solution of procaine hydrochloride was injected deep into each muscle to be operated on, so that no conjunctival infiltration occurred. A single silk traction suture was placed near the limbus on the side of the muscle to be operated on. After operation, binocular occlusion was used for five days with patients both of whose horizontal rectus muscles were operated on or on whom a resection was done and for three days with patients on whom only a recession was performed. In all but 1 patient only one eye was operated on at a time. Conjunctival sutures were removed on the fifth postoperative day. When the reaction had subsided and the eye had paled, measurements of the residual angle of deviation were made in exactly the same manner as that employed in the original examination.

AMOUNT OF CORRECTION OBTAINABLE BY OPERATION

Theoretically, 1 mm. of movement of the eyeball should move the optic axis 5 degrees of arc. This value is based on the fact that the circumference of the eyeball is 72 mm. Movement of the insertion of a single muscle 1 mm. should result in the optic axis being moved half that amount unless it is balanced by a movement of the antagonistic muscle in the opposite direction to the same degree. However, the theoretic degree of correction of a muscle does not agree with that observed in practice, owing to such factors as the fascial attachments, the relative strength of the muscles, the muscle operated on and the convergence-divergence relation. In patients with monocular concomitant squint, if one eye is constantly held in one position, either of convergence or of divergence, there is an inhibitional (Chavasse) lack of ability to rotate the eye completely in the opposite direction even if the nonsquinting eye is occluded. This defect is innervational and does not represent a true paresis, but it does affect the relative strength of the two muscles.

Lancaster [1] pointed out that movement of the insertion of a single muscle 1 mm. results in a change of 4 prism diopters of deviation for squints of small degree. In a large eye 1 mm. of shift of the center of the cornea results in a correction of less than 5 degrees,[2] while in a smaller eye such a shift results in a correction of more than 5 degrees. Wiener and Alvis [3] expressed the opinion that 1 mm. of change in the muscle insertion results in a change of roughly 10 prism diopters (approximately 5 degrees of change), if balanced by operation on the opposing muscle.

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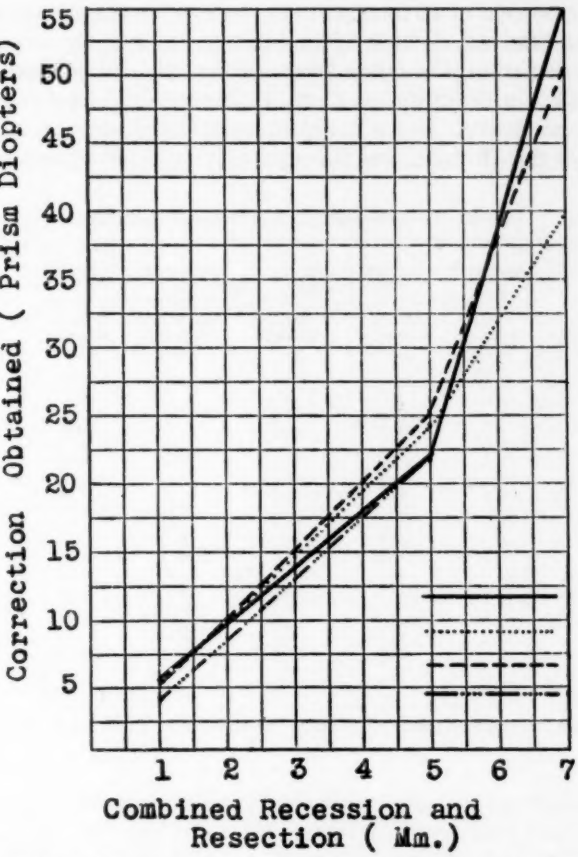
1. Lancaster, W. B.: Graduate Lecture read at the meeting of the American Academy of Ophthalmology and Otolaryngology, 1940.

2. Lancaster, W. B., in Berens, C.: The Eye and Its Diseases, Philadelphia, W. B. Saunders Company, 1936, p. 1136.

3. Wiener, M., and Alvis, B. Y.: Surgery of the Eye, Philadelphia, W. B. Saunders Company, 1939, p. 356.

It is obvious that there is a difference in the amount of correction obtained depending on whether the operation is a lengthening or a shortening process and on whether the internal or the external rectus muscle is concerned. Jameson [4] stated that 1 mm. of recession results in 5 degrees of correction if done on the internal rectus muscle and in only 2 degrees of correction if done on the external rectus muscle. In other words, a 5 mm. recession of the internus rectus muscle would result in 20 to 25 arc degrees of correction, and a 5 mm. recession of the



Graphic representation of the average correction (for a distance of 20 feet [60 cm.]) obtainable by combined resection and recession of the horizontal rectus muscles.

In this figure, values for alternating convergent strabismus are indicated by a solid line; values for monocular divergent strabismus, by a line of dots; values for monocular convergent strabismus, by a broken line, and values for alternating divergent strabismus, by a line of dots and dashes.

externus rectus muscle would give one-third that correction. Worth [5] stated that 1 mm. of recession corrected 4 degrees of deviation if done on the internus rectus muscle and 2 degrees of deviation if done on the externus rectus muscle. Gifford [6]

4. Jameson, P. C.: Entity of Muscle Recession, Arch. Ophth. **21**:362 (Feb.) 1939.

5. Worth, C.: Worth's Squint, ed. 7, edited by F. Bernard Chavasse, Philadelphia, P. Blakiston's Son & Co., 1939, p. 583.

6. Gifford, S. R.: A Textbook of Ophthalmology, Philadelphia, W. B. Saunders Company, 1938, p. 393.

expressed the belief that 1 mm. of recession corrected 3 degrees of deviation if done on the internus rectus muscle and only 1.5 degrees if done on the externus rectus muscle. According to Peter,[7] 5 mm. of recession in a case of convergent squint corrects 11 to 12 degrees of deviation at the most, and with good technic, a combined recession and advancement may give a net correction of as much as 25 degrees, although in most cases it may be 5 to 7 degrees less.

Dunnington and Wheeler[8] found that the average correction resulting from a single recession of 4 mm. was 7.3 prism diopters. With a simultaneous recession of 4 mm. and a resection of 10 mm. on the same eye, an average of 40 prism diopters of correction was obtained. Gibson[9] found that in cases of convergent squint with 10 to 20 degrees of deviation, 4 to 6 mm. of correction, divided between the two muscles, was necessary. For a deviation of 25 to 35 degrees he found 6 to 8 mm. of total correction to be necessary. For a deviation of 40 to 50 degrees he recommended a total correction of 9 to 10 mm., and for squint of over 50 degrees, a total correction

TABLE 1.—*Alternating Convergent Strabismus*

	Initials	Age, Yr.	Deviation (Esotropia)		Recession of Internal Rectus Muscle, Mm.	Resection of External Rectus Muscle, Mm.	Residual Deviation (Esotropia)	
			Distant Vision, Δ	Near Vision, Δ			Distant Vision, Δ	Near Vision, Δ
1	O. F. W.	28	45	54	5	7	9	16
2	O. F. W.	28	9	16	..	4	0	12
3	R. A. B.	20	10	20	5	..	0	0
4	R. H.	24	20	20	..	6	10	10
5	E. T. C.	23	20	20	4	4	0	0
6	O. E.	20	46	55	5	6	16	23
7	O. E.	20	16	23	5	..	10	12
8	O. E.	20	10	12	..	5	0	0
9	L. A. G.	24	32	36	5	5	12	12
10	L. A. G.	24	12	12	..	6	0	0
11	O. H.	35	33	30	5	5	10	12*
12	E. G. Z.	25	34	34	5	5	8	8†
13	E. G. Z.	25	8	8	..	3	3	3†
14	E. D. W.	21	16	20	5	..	4	8
15	E. D. W.	21	4	8	3	..	5‡	0
16	M. W. H.	29	24	18	..	5	9	9
17	M. W. H.	29	9	9	2	..	0	0
18	C. E. G.	22	67	67	7	7	12	12
19	C. E. G.	22	12	12	4	..	0	0

* High plus angle κ.
† Diplopia following orthoptics; residual deviation corrected with prism base out.
‡ High angle.

of 12 mm. He observed that under identical conditions more correction was usually attained by combined recession and resection on one eye than by bilateral recession.

My own results indicate a significant variation in the amount of correction obtainable with the same amount of resection or recession of either of the horizontal rectus muscles. The present series of 65 operations are classified as follows, the average amount of correction obtained for each millimeter, 5 mm. and, in combined operations, 7 mm. of recession or/and resection being indicated after each type. These values, it should be noted, are not absolute, but have served as excellent guides in successful treatment in subsequent cases:

Convergent Squint.—(*a*) Alternating Type (19 operations; table 1): Each millimeter of recession of the internal rectus muscle resulted in a correction averaging

7. Peter, L. C.: Present Status of Tendon Transplantation of the Ocular Muscles, Am. J. Surg. **42**:30, 1938.

8. Dunnington, J. H., and Wheeler, M. C.: Operative Results in Two Hundred and Eleven Cases of Convergent Strabismus, Arch. Ophth. **28**:1 (July) 1942.

9. Gibson, G. G.: Analysis of Operative Results in Concomitant Strabismus, Arch. Ophth. **23**:477 (March) 1940.

2.4 prism diopters for distance and 3 prism diopters for near vision (for 6 recessions of 2 to 5 mm. each). A 5 mm. recession of the internal rectus muscle alone resulted in a correction averaging 9.3 prism diopters for distance and 14.3 prism diopters for near vision.

Each millimeter of resection of the external rectus muscle resulted in correction averaging 1.9 prism diopters for distance and 1.8 prism diopters for near vision (for 6 resections of 3 to 6 mm.). A 5 mm. resection of the external rectus muscle alone resulted in a correction averaging 9.5 prism diopters for distance and 10.5 prism diopters for near vision.

Each millimeter of combined recession of the internal rectus muscle and resection of the external rectus muscle (7 operations) resulted in an average correction of 2.8 prism diopters for both distance and near vision (for 4 to 7 mm. of correction of each muscle). The correction obtained from a combined 5 mm. resection and recession on each muscle averaged 23 prism diopters for distance and 22.6 prism

TABLE 2.—*Monocular Convergent Strabismus*

Initials	Age, Yr.	Deviation (Esotropia)		Recession of Internal Rectus Muscle, Mm.	Resection of External Rectus Muscle, Mm.	Residual Deviation (Esotropia)	
		Distant Vision	Near Vision			Distant Vision	Near Vision
1 J. B. L.	33	40° *	40°	7	7	15°	15°
2 J. B. L.	33	15°	15°	5	5	0	0
3 R. T.	22	30°	28°	5	3	22°	18°
4 R. T.	22	22°	18°	5	6	0	0
5 J. T. M.	22	30°	30°	7	8	17°	13°
6 J. T. M.	22	17°	13°	5	5	0	0
7 A. C. D.	21	6△	16△	5	3	0	3△
8 H. L. S.	24	10°	10°	5	5	0	7△†
9 F. L. B.	27	36△	36△	5	5	12△	12△
10 F. L. B.	27	12△	12△	..	5	0	0
11 D. W. B.	24	37△	37△	5	5	12△	12△
12 D. W. B.	24	12△	16△	4	..	7△	6△
13 D. W. B.	24	7△	6△	..	4	0	0
14 S. M. S.	26	30△	26△	5	..	9△	9△‡
15 R. A. E.	49	65△	65△	7	7	12△	10△
16 R. A. E.	49	12△	10△	5	..	0	0
17 E. H. C.	25	18△	23△	5	5	0	0
18 M. H. F.	22	34△	38△	6	6	4△	7△
19 M. H. F.	22	4△	7△	2	..	3△	3△
20 M. A. C.	22	25°	25°	7	7	0	0

* Although not strictly accurate, 1 arc degree is taken to be equal to 2 prism diopters.
† Exotropia.
‡ High angle κ.

diopters for near vision. In a single case a combined 7 mm. resection and recession on each muscle resulted in 55 prism diopters of correction for both distance and near vision.

(*b*) Monocular Type (20 operations; table 2): Each millimeter of recession of the internal rectus muscle resulted in correction averaging 2.4 prism diopters for distance and 2.5 prism diopters for near vision (for 4 recessions of 2.5 mm.). A 5 mm. recession of the internal rectus muscle alone resulted in a correction averaging 16.5 prism diopters for distance and 13.5 prism diopters for near vision.

Each millimeter of resection of the external rectus muscle resulted in correction averaging 2.1 prism diopters for distance and 2 prism diopters for near vision (for 2 resections of 4 to 5 mm.). A 5 mm. resection of the external rectus muscle alone resulted in a correction of 12 prism diopters for both distance and near vision.

Each millimeter of combined recession of the internal rectus muscle and resection of the externus rectus muscle (14 operations) resulted in a correction averaging 2.7 prism diopters for distance and 2.8 prism diopters for near vision (for 3 to 7 mm. of correction of each muscle). The correction obtained from a combined 5 mm.

resection and recession on each muscle averaged 25.1 prism diopters for both distance and near vision. For a combined 7 mm. resection and recession on each muscle an average correction of 51 prism diopters for distance and 51.6 prism diopters for near vision was obtained.

Divergent Squint.—(*a*) Alternating Type (17 operations): Each millimeter of recession of the external rectus muscle alone resulted in correction averaging 2.7 prism diopters for both distance and near vision (for 3 recessions of 5 to 7 mm.). A 5 mm. recession of the external rectus muscle alone resulted in a

TABLE 3.—*Alternating Divergent Squint*

	Initials	Age, Yr.	Deviation (Exotropia) Distant Vision, △	Deviation (Exotropia) Near Vision, △	Recession of Internal Rectus Muscle, Mm.	Resection of External Rectus Muscle, Mm.	Residual Deviation (Exotropia) Distant Vision, △	Residual Deviation (Exotropia) Near Vision, △
1	R. F. F.	24	24	24	5	5	9	10
2	E. T.	23	30	40	..	5	14	20
3	E. T.	23	14	20	..	5	0	0
4	L. O. H.	26	25	32	5	..	20	10
5	G. J. H.	22	28	18	6	6	8	4
6	M. P. K.	29	47	49	..	5	32	33
7	M. F. K.	29	32	33	3	5	23	23
8	M. F. K.	29	23	23	5	..	7	0
9	O. J. S.	23	60	60	6	5	34	34
10	A. E. K.	27	20	20	..	6	3	7
11	T. A. R.	22	36	5	7	..	10	3
12	P. H. S.	24	26	26	7	6	9	0
13	M. U.	26	25	25	5	5	10	10
14	M. U.	26	10	10	..	3	0	0
15	A. E. A.	27	35	35	5	5	6	4
16	J. B. S.	24	35	40	5	5	0	4
17	H. R. P.	21	22	35	5	5	0	2

TABLE 4.—*Monocular Divergent Squint*

	Initials	Age, Yr.	Deviation (Exotropia) Distant Vision	Deviation (Exotropia) Near Vision	Recession of External Rectus Muscle, Mm.	Resection of Internal Rectus Muscle, Mm.	Residual Deviation (Exotropia) Distant Vision	Residual Deviation (Exotropia) Near Vision
1	R. J. T.	21	12△	22△	6 *	..	4△	0
2	H. W. W.	31	20°	20°	6	6	9°	9°
3	H. W. W.	31	9°	9°	..	6	4°	3°
4	R. C. R.	26	12°	12°	5	5	0	0
5	E. C. D.	33	25°	25°	6	7	8°	8°
6	E. C. D.	33	8°	8°	3	4	0	0
7	W. S.	24	65△	65△	6	6	17△	17△
8	W. S.	24	17△	17△	..	5	0	0
9	H. V. M.	29	20°	20°	7	7	0	0

* Both external recti.

correction averaging 10.5 prism diopters for distance and 22.5 prism diopters for near vision.

Each millimeter of resection of the internal rectus muscle alone resulted in correction averaging 3 prism diopters for distance and 3.2 prism diopters for near vision (for 5 resections of 3 to 6 mm.). A 5 mm. resection of the internal rectus muscle alone resulted in a correction averaging 15 prism diopters for distance and 18.6 prism diopters for near vision.

Each millimeter of combined recession of the external rectus muscle and resection of the internal rectus muscle (9 operations) resulted in a correction averaging 2 prism diopters for distance and 2.1 prism diopters for near vision (for 3 to 7 mm. of correction of each muscle). The correction obtained from a combined

5 mm. operation on each muscle averaged 23.2 prism diopters for distance and 25.8 prism diopters for near vision.

(*b*) Monocular Type (9 operations): Recession of the external rectus muscle alone resulted in 0.6 prism diopter of correction for distance and 22 prism diopters of correction for near vision (for 6 mm. resection of each external rectus muscle in 1 case).

Each millimeter of resection of the internal rectus muscle alone resulted in correction averaging 2 prism diopters for distance and 2.6 prism diopters for near

TABLE 5.—*Summary of Average Corrections Obtainable by Resection and/or Recession of the Horizontal Rectus Muscles*

Types of Operation	Convergent Strabismus		Divergent Strabismus	
	Alternating	Monocular	Alternating	Monocular
Recession of internal rectus muscle (alone)				
1 mm.	2.4△ distance 3.0△ near vision	2.4△ distance 2.5△ near vision		
5 mm.	9.3△ distance 14.3△ near vision	16.5△ distance 13 △ near vision		
Resection of internal rectus muscle (alone)				
1 mm.	.....	.....	3.0△ distance 3.2△ near vision	2.0△ distance 2.6△ near vision
5 mm.	.....	.....	15 △ distance 18.6△ near vision	17 △ distance 17 △ near vision
Recession of external rectus muscle (alone)				
1 mm.	.....	.....	2.7△ distance 2.7△ near vision	0.6△ distance 1.8△ near vision
5 mm.	.....	.....	10.5△ distance 22.5△ near vision	
Resection of external rectus muscle (alone)				
1 mm.	1.9△ distance 1.8△ near vision	2.1△ distance 2.0△ near vision		
5 mm.	9.5△ distance 10.5△ near vision	12 △ distance 12 △ near vision		
Combined operations on external and internal rectus muscles of one eye				
Each 1 mm.	2.8△ distance 2.8△ near vision	2.7△ distance 2.8△ near vision	2.0△ distance 2.1△ near vision	2.7△ distance 2.7△ near vision
1 mm. both muscles	5.6△ distance 5.6△ near vision	5.4△ distance 5.6△ near vision	4.0△ distance 4.2△ near vision	5.4△ distance 5.4△ near vision
5 mm. each muscle	23 △ distance 22.6△ near vision	25.1△ distance 25.1△ near vision	23.2△ distance 25.8△ near vision	24 △ distance 24 △ near vision
7 mm. each muscle	55 △ distance 55 △ near vision	51.0△ distance 51.6△ near vision	....	40 △ distance 40 △ near vision

vision (for 2 resections of 5 to 6 mm.). A single 5 mm. resection of the internal rectus muscle alone resulted in a correction averaging 17 prism diopters for both distance and near vision.

Each millimeter of combined recession of the external rectus muscle and resection of the internal rectus muscle (6 operations) resulted in a correction averaging 2.7 prism diopters for both distance and near vision (for 3 to 7 mm. of correction of each muscle). The correction obtained from a single combined 5 mm. operation on each muscle was 24 prism diopters for both distance and near vision. From a single combined 7 mm. operation on each muscle, the correction was 40 prism diopters for both distance and near vision.

Comment.—From table 5 it is evident that the average values are fairly consistent. Resection of the internal rectus muscle resulted in more correction than did recession of that muscle, while the opposite result was obtained with operation on the external rectus muscle, on which recession was generally more effective. Combined resection and recession resulted in approximately the same amount of correction for all four categories of squint considered. The most interesting result derived from this series of operations is the fact that with an equal resection and recession of 7 mm. each the amount of correction was approximately twice that obtained with an equal resection and recession of 5 mm. each. This is undoubtedly related to changes in the subsidiary duction action of the superior and inferior rectus muscles. At any rate, it negates any possible consideration of the theoretic value of 5 arc degrees of correction for 1 mm. of shift in the optic axis.

It will be noted that recessions of 7 mm. were done in some cases in spite of the fact that it is a standard procedure not to do a recession of the internal rectus muscle of more than 5 mm. or one of the external rectus muscle of more than 3 mm. Jameson [4] stated that 1.5 to 2 mm. can be added to the recession spaces if the eyeball is large. It has been my feeling that whenever possible correction of the deviation should be divided between the two horizontal muscles of the eye to be operated on and that in cases of large angles of squint, especially of the alternating type, correction of the deviation should be divided between the two eyes. In doing this I have noted less tendency to produce abnormal amounts of traction on one muscle. A recession of 7 mm. of either muscle when combined with a 7 mm. resection of its opponent did not interfere with the motility of the eye in any case.

Although the values found in this series pertain to adults with nonaccommodative squint, the same values were obtained for a small number of children and for adults with accommodative squint who were operated on during the same period.

To determine whether there is any difference between the correction obtained when one operates on the deviating eye in a case of monocular squint and that obtained when the fixing eye is operated on, the results of operation on patients with monocular squint (tables 2 and 4) who had both eyes operated on (at different times) were compared. For 7 patients with monocular convergent squint the average correction was 2.7 prism diopters for distance and 2.8 prism diopters for near vision for each millimeter of operation on the muscles of the deviating eye and 2.8 prism diopters for distance and 2.6 prism diopters for near vision for each millimeter of correction of the muscles of the nondeviating eye. For 3 patients with monocular divergent squint the average correction was 2.8 prism diopters for distance and near vision for each millimeter of operation on the muscles of the deviating eye and 2.8 prism diopters for distance and 2.4 prism diopters for near vision for each millimeter of operation on muscles of the deviating eye. Thus it appears that there was no difference between the amount of correction obtained from operation on the deviating eye and that obtained from operation on the nondeviating eye in cases of monocular squint.

GUIDES TO THE SELECTION OF THE PROPER MUSCLE FOR OPERATION

In order to choose the proper surgical procedure in cases of concomitant squint, it is important to determine the nature of each case, especially as regards the relative state of convergence and divergence and the angle of deviation for distance and for near vision. With high degrees of deviation equal amounts of recession and resection of the muscles of the deviating eye are indicated, the amount usually being divided between the two eyes if the deviation is over 25 to 30 degrees. This is particularly true in cases of monocular squint in which the visual acuity of the

deviating eye is very low. In these cases the relative near point of convergence is not of as much importance, since the degree of deviation is rather constant for distance and for near vision. With smaller degrees of squint, the relative near point of convergence is of extreme importance and is the deciding factor in the decision as to which muscle or muscles should be operated on. The following plans of treatment are based on these considerations, together with the guiding values as to the amounts of correction obtainable with the operative procedures previously mentioned.

Convergent Squint.—When the deviation for near vision is significantly greater than that for distance and the relative convergence near point is close, the deviation is of the convergence excess type. Recession of the internal rectus muscle should be the primary procedure. In cases of monocular squint the deviating eye should be operated on first, while in cases of alternating squint the eye which turns in longest on attempting to converge should be operated on first.

When the deviation for distance is greater than that for near vision and the relative convergence is poor, the deviation is of the convergence insufficiency type. Resection of the external rectus muscle of the deviating eye should be the primary procedure.

Convergence Excess Type: For deviations up to 15 prism diopters recession of the internal rectus muscle of the deviating eye is indicated. For deviations of 12 to 25 prism diopters recession of the internal rectus muscle and resection of the external rectus muscle of the deviating eye, in proportions indicated by the values obtained in the first portion of this paper, should be performed.

Convergence Insufficiency Type: For deviations up to 16 prism diopters resection of the internal rectus muscle of the deviating eye is indicated. For deviations of 16 to 25 prism diopters resection of both internal rectus muscles or resection of the internal muscle of the deviating eye and recession of the external rectus muscle of the same eye, depending on the deviations for distance and near vision, are indicated.

Deviations above these amounts require combined operations on the deviating eye and later correction of the other eye for the residual deviation.

Divergent Squint.—When the deviation for distance is greater than that for near vision, the squint is considered to be of the divergence excess type. Recession of the external rectus muscle of the deviating eye should be the primary operation. When the deviation for distance is less than that for near vision, it is considered to be of the divergence insufficiency type. Resection of the internal rectus muscle is then the primary operation. In cases of alternating squint the eye which turns out first in an attempt to converge should be considered as the deviating eye.

Divergence Excess Type: For deviations up to 10 or 11 prism diopters recession of the external rectus muscle of the deviating eye is indicated. For deviations of 10 to 20 prism diopters recession of both external rectus muscles or recession of the external rectus muscle of the deviating eye and resection of the internal rectus muscle of the same eye, depending on the deviations for distance and for near vision, are indicated.

Divergence Insufficiency Type: For deviations up to 12 prism diopters resection of the external rectus muscle of the squinting eye is indicated. For deviations of 12 to 20 prism diopters resection of both external rectus muscles is indicated. For deviations of over 20 prism diopters, resection of the external rectus muscle and recession of the internal rectus muscle of the deviating eye, in the proportions indicated, should be done.

In a majority of cases of considerable deviation the measurements for distance and for near vision are the same. Here equal amounts of recession and resection are best. In cases of monocular squint it is my policy to do most, or all, of the correction on the deviating eye, up to 7 mm. of correction on each of the horizontal rectus muscles, and to divide the correction for residual deviation between the horizontal rectus muscles of the other eye.

It must be pointed out that one should not be guided wholly by stereotyped tables, but such data can be of definite help to the beginner. One must determine the type of deviation and its measurement for distance and for near vision, with and without correcting lenses and in the cardinal directions of gaze. In addition, the motility, the convergence ability and the retinal correspondence must be determined in every case in order to make proper use of the guiding principles already indicated.

PUPILLARY REFLEX TO DARKNESS

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In 1939 one of us (Lowenstein [1]) described a pupillary reflex which he called the "reflex to darkness." In order to elicit this reflex both eyes of the subject tested are adapted to a constant level of illumination in which darkness is a periodic stimulus. Two small lamps separated from each other by a screen (so that the right eye cannot see the left lamp and vice versa) burn continuously for a period of twelve minutes, which is the time necessary for adaptation. The light of one or the other of these lamps is periodically interrupted by a motor interrupter for one second.[2] During the test the patient fixes on a nonluminous point in the distance. The resulting movements of the pupils are recorded by pupillography.

The reflex to darkness is manifested both directly and consensually. The pupillographic representation of a normal reflex to darkness is shown schematically in chart 1. The pupils had been adapted to light in the period preceding time *A*. The period of unilateral stimulation by darkness lasts from *A* to *B*. The pupil dilates during this period after a latency period. When at *B* the former level of illumination is restored bilaterally, the pupil responds with a contraction and redilation. The period from *A* to *B* is called the primary reaction, or primary dilation. The period from *B* to *C* is called the secondary reaction and consists of contraction (*c* to *d*) and secondary redilation (*d* to *e*).

Actual records of the reflex to darkness in human beings and animals are shown in figure 2 and figure 5 *A*. Figure 2 shows a reflex to darkness (*III*) compared with the reflexes to light (*I*) and to near and far vision (*II*) in the same subject.

In comparative pupillographic studies it was shown that the reaction to darkness occurs in the monkey, cat, rabbit and pigeon as well as in man. The secondary redilation, however, is fully developed only in man. There are occasional suggestions of a secondary redilation in the monkey, but it is constant only in man.

In man and in all the species of animals examined, a definite relationship can be demonstrated between the magnitude of the reactions to light, to darkness and to near vision. The extent of the contraction in the light reflex is about equal to that produced in the reaction to near vision. The ratio of this contraction to the dilation phase of the reaction to darkness is about 9 to 2 (fig. 2). The extent of dilation to darkness in its primary phase is about one half of the extent in diameter of the subsequent contraction when the darkness stimulus has ended. However, a comparison of the latter depth of contraction to that seen in a normal reaction to light shows it to be only about one third as great in extent.

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Pupillographic Studies: IV. From the Neurologic and Ophthalmologic Departments of New York University College of Medicine.

1. Lowenstein, O.: Les troubles du réflexe pupillaire à la lumière dans les affections syphilitiques du système nerveux central, Paris, Gaston Doin & Cie, 1939.

2. Lowenstein, O., and Friedman, E. D.: Present State of Pupillography: Its Method and Diagnostic Significance, Arch. Ophth. **27**:969 (May) 1942.

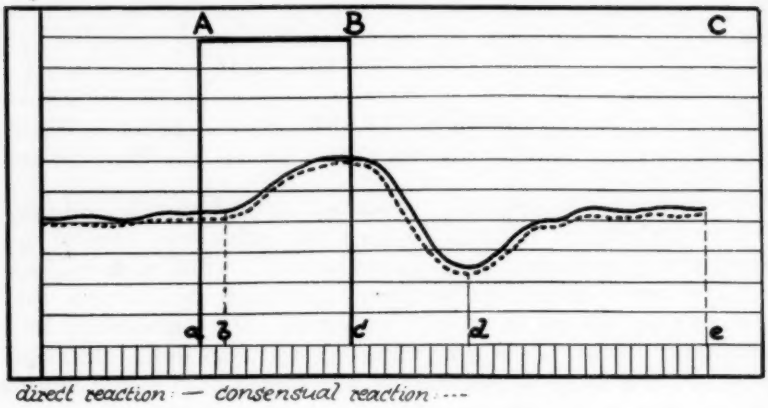

Fig. 1.—Pupillary reaction to darkness (schematic). The space to the left of *A* represents adaptation to light. *A* to *B* represents unilateral stimulation by darkness. Both pupils dilate (primary phase of dilation) after a latency period (*a* to *b*). The space on the right to *B* represents the same light conditions as those in effect before use of the darkness stimulus. From *c* to *d* is the primary contraction phase (greater than the preceding dilation) and from *d* to *e* the secondary dilation phase.

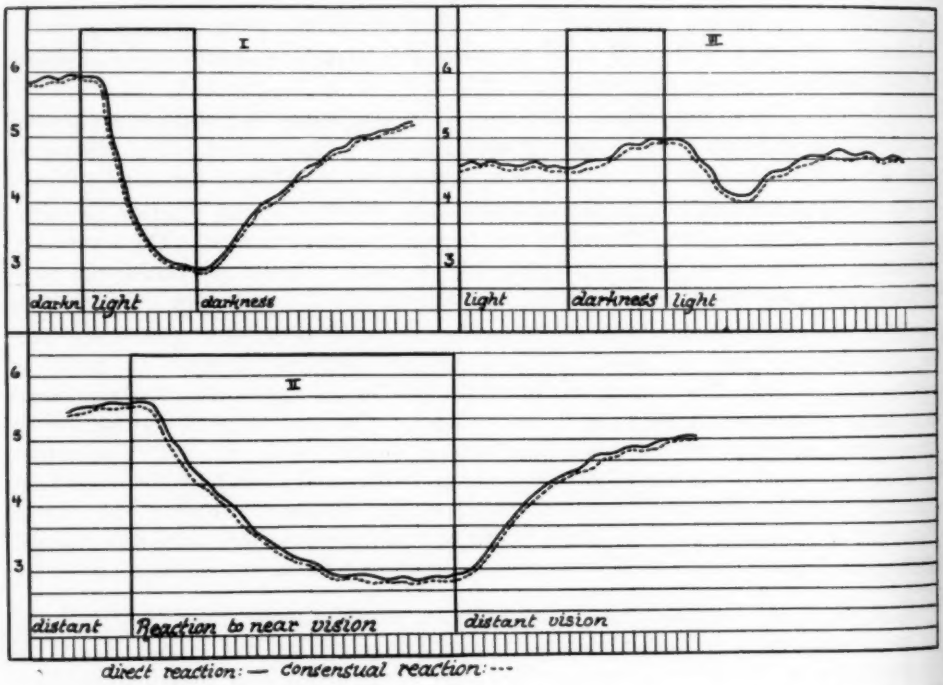

Fig. 2.—Reflex to darkness (*III*) as compared with that to light (*I*) and to near and far vision (*II*) in the same person.

In each species of animals examined there is a characteristic relationship between the change in pupillary diameter in the contraction phase of the light reflex and the dilation phase of the reflex to darkness. In all animals studied so far, the ratio of the darkness reflex to the light reflex was greater than it is in man. It is at its maximum in the cat, in which it may be up to 1 to 1 (fig. 3). The extent of pupillary contraction following the dilation to darkness has been about the same as the primary dilation to darkness in all animals examined to date. There is, therefore, no need for a redilation following the contraction. In man, however, since the contraction following the dilation to darkness is greater in extent than the preceding dilation, a secondary dilation has to take place. Secondary redilation exists therefore only in man.

It has long been known that in man the redilation following the contraction to light may under pathologic conditions be absent. The so-called neurotonic pupil, characterized by a good contraction to light which is not followed by an equivalent redilation, has been described in the literature from time to time. It is

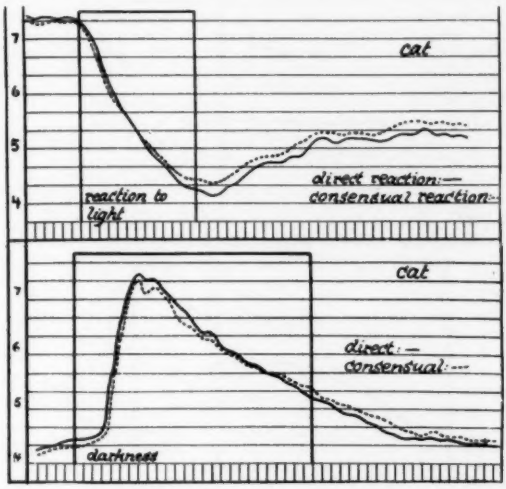

Fig. 3.—Reflex to light and darkness in a cat. The extent of the dilation to darkness is about the same as that of the contraction to light. (The ratio is generally between 1 to 1 and 1 to 2.)

ordinarily considered to be an infrequent condition. However, in pupillographic examinations it is more frequently found than would be expected.

The first line of figure 4 illustrates the fact that a pupil, although it cannot redilate immediately after a contraction to light, may be able to contract further after a second or a third light stimulus. The picture of "descending pupil" of Lowenstein develops. On the other hand, cases have been noted in which the contraction is rather poor but the redilation is good. After repeated stimulation by light, the pupillary diameter is increased over its original size ("climbing pupil" of Lowenstein). These conditions show that more complex factors are involved in the redilation after contraction to light than simple relaxation within the area of the third cranial nerve. Under pathologic conditions these factors may outweigh the action of the third nerve.

Whereas the reflex to darkness may frequently disappear completely concomitantly with the reflex to light, as with the Argyll Robertson or absolute fixed pupil,

there are cases demonstrating a certain independence of the two reflexes from one another. A case of neurotonic pupil in which the redilation after contraction to light was absent but the primary dilation in the darkness reflex was present has been reported.[3] Other cases have been observed in which the primary reaction to darkness was absent but the reflex to light was present in both of its phases. Figure 5 shows a graphic summary of some possible modifications of the darkness reflex as it has actually been observed in pathologic conditions. In *A* a normal reflex to darkness is shown. In *B 1* the primary dilation, which is of normal extent, is preceded by a preliminary contraction in a case of anisocoria. In *B 2* the primary dilation is absent, while secondary contraction and redilation are normal. In *B 3* the secondary phase is absent in the reaction of the directly stimulated pupil but present in the consensually reacting pupil. In *B 4* the secondary dilation phase is absent, while primary dilation and subsequent contraction are present. *B 3* and *B 4* show anisocoria.

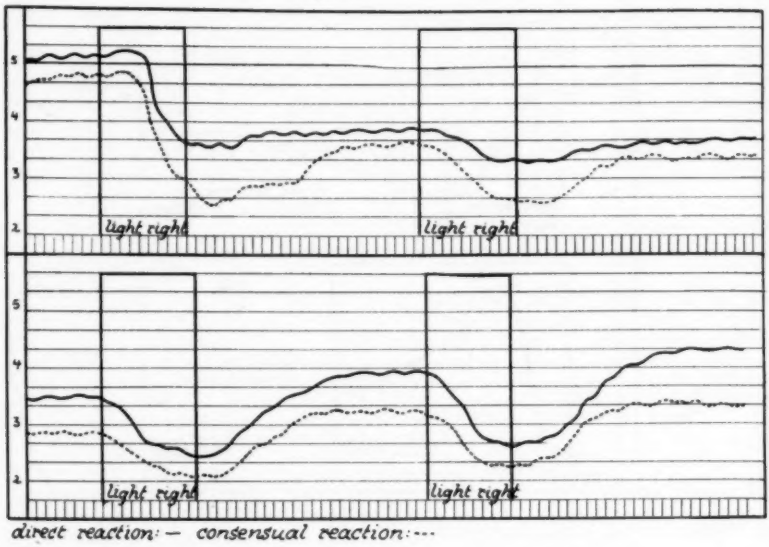

Fig. 4.—First line, "descending pupil"; second line, "climbing pupil."

We are able to state that the reflex to darkness is frequently more susceptible to the influence of pathologic conditions than is the reflex to light. We have found modifications of the reflex to darkness more frequently than of the reflex to light in cases in which neurologic lesions were known to exist. It is interesting to note that in man the secondary dilation phase is the portion of the reflex to darkness most prone to disappear (fig. 5, *B 4*) when a pathologic condition is present, a fact which perhaps indicates that the phylogenetically youngest part is the most vulnerable one. Any of the abnormal patterns of the darkness reflex may coexist with either a perfectly normal reflex to light or a pathologic one. The deviations from normal in the light reflex may seem to be contrary to the abnormal features of the reflex to darkness or may be consistent with them. We may say, then,

3. Lowenstein, O., and Friedman, E. D.: Adie's Syndrome (Pupillotonic Pseudotabes), Arch. Ophth. **28**:1042 (Dec.) 1942.

that there is some independence of the two reflexes from one another, but, on the other hand, the same lesion may be able to destroy them both, in whole or in part.

These dissociations of the two reflexes suggest that the reflex to darkness is more than a simple reversal of the reflex to light. Such a supposition as this is not an unusual concept to psychologists, who have emphasized the fact that a short interruption of a constant stimulus is effective as a new stimulus.

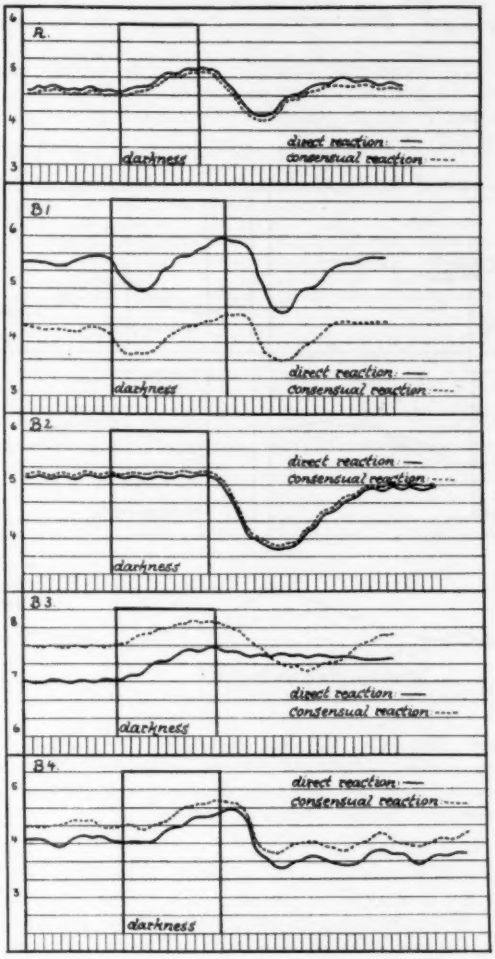

Fig. 5.—Pathologic variations of the reflex to darkness (*A* shows the normal reflex): *B1*, dilation preceded by a preliminary contraction; *B2*, primary dilation absent and the secondary phase normal; *B3*, the secondary phase absent in the directly stimulated pupil; *B4*, the secondary dilation phase absent (monkey type).

We are unable to say anything definite as to the anatomic basis of the dissociation. The types of pathologic disturbances and dissociations described point to the likelihood that both common and separate pathways are utilized in the reflexes to light and to darkness.

We wish to report a case which may shed a little light on the problem of the nervous pathways through which the reflex to darkness travels:

The patient, a youth aged 18, had been suffering from headaches and diplopia for approximately five months. He had had disturbances of his gait, mental dulness and vomiting for two or three weeks.

When examined on Jan. 3, 1941, he showed 2 D. of papilledema in each eye, a limitation of upward gaze and fixation of the pupils to light and convergence. Ventriculography confirmed the clinical diagnosis of tumor of the pineal body.

On January 5 he was operated on by Dr. John B. Scarff. The pineal body was exposed by an approach along the falx, and a total gross removal of a fairly firm, lobulated, well demarcated tumor was done. Postoperatively, there was a transient episode of psychotic behavior.

On April 5, 1942 it was found that clinically the pupils did not react to light but reacted to convergence promptly (Argyll Robertson phenomenon). Both optic disks showed temporal pallor. There was marked irregular concentric contraction of the visual fields of both eyes. The vision was 20/20 in both eyes.

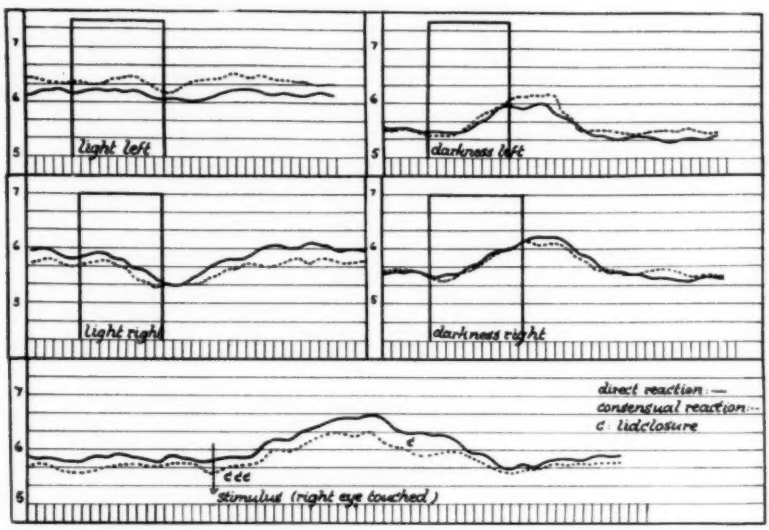

Fig. 6.—The pupillary reflexes in the case reported. The first line shows that the reflex to light is absent and the reflex to darkness present on the left side; the second line, that the reflex to light is diminished and the reflex to darkness exaggerated on the right side, and the third line, that the sensory dilation reflex is normal.

On July 7 the pupils still showed the same behavior. The fields of both eyes had improved. There was a paresis of the left superior rectus muscle. The pupil again showed an Argyll Robertson phenomenon. When the patient attempted to look upward and to the left his left eyeball underwent retraction and propulsion about four times (rotatory nystagmus). During this period the right eye displayed coarse and slow nystagmoid motions.

Pupillographic Studies.—The reflex to light was absent on the left side and greatly diminished on the right side. The light reaction of the right pupil amounted to 0.66 mm. The consensual reaction of the left pupil, which did not react to direct stimulation by light, amounted to about 0.33 mm. The reaction to light of the right pupil was sluggish and had a latency period of about 0.5 second (normal, less than 0.3 second). It is striking that the second light stimulus and all subsequent ones in a series of repeated stimulations provoked reactions to light which were more rapid than the first one. Nevertheless, the reaction did not become more extensive than 0.5 mm. on either side.

Stimulation by sound provoked a dilation on both sides of about 1.3 mm. The psychosensory restitution phenomenon was fairly effective on both sides after a sound stimulus; for example, both pupils reacted to light to an extent of about 0.66 mm. and the latency period decreased to 0.4 second from its former level of 0.5 second.

The spontaneous lid closure reflex was absent. The pupillary reflex to conjunctival stimulation, however, was present and showed a fully developed dilatation. The reaction to near vision was present.

Primary dilation to darkness was present and about equal in the two eyes. It amounted to 1 mm. or more (fig. 6). The secondary phase of the reflex to darkness was present, but the secondary redilation phase was absent (a configuration found in the monkey).

We wished to know whether or not Argyll Robertson pupil (on a nonsyphilitic basis) is associated in all cases with an undiminished, or perhaps even an exaggerated, reflex to darkness. We therefore examined another patient, a 22 year old man with a tumor of the superior colliculus. He displayed a fully developed Argyll Robertson pupil, with paralysis of upward gaze. The reflex to darkness was absent.

CONCLUSION

In a patient operated on for pinealoma, we observed a dissociation between the reflexes to light and to darkness. The former were practically absent, and the latter were exaggerated.

This dissociation of pupillary reflexes suggests the existence of separate pathways for the reactions to light and to darkness. We cannot precisely localize the lesion in the pathways of the light reflex in the case reported, since no anatomic evidence is available.

We can state, however, that there must exist at least one point in the brain where the pathways of the reflexes to light and to darkness are not identical. This dissociation between the reflexes to light and darkness is not a universal characteristic of the nonsyphilitic Argyll Robertson phenomenon, since it was not demonstrable in a case of Argyll Robertson phenomenon due to a tumor of the superior colliculus.

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GENETIC STUDIES ON ECTOPIA LENTIS

A PEDIGREE OF SIMPLE ECTOPIA OF THE LENS

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The present report on the inheritance of ectopia lentis is based on the study of a single kindred displaying this relatively rare ocular anomaly. The pedigree includes six generations, the first two of which are known only from historical evidence supplied by the descendants. A total of 157 of the descendants were examined in their homes or in the University Hospital ophthalmic clinic, where slit lamp and refraction facilities were available. Twenty-four with ectopia lentis were observed, and the history of 5 other persons suggested probable dislocation of the lenses. In addition, 2 unaffected members were regarded as gene carriers, since they possessed affected children and grandchildren.

Besides the ocular examinations of members of the various families belonging to this kindred, several other tests and measurements were made, including anthropometric measurements, serologic tests of blood and saliva, determination of the taste reaction to phenylthiocarbamide, tests of color vision and eye dominance, tests of handedness and dermatoglyphic studies of the fingers, palms and soles. Blood samples were tested with respect to the blood groups (O, A_1, A_2, B), the MN blood types and the Rh factor of Landsteiner and Wiener.[1] The "secretor factor" was determined on the saliva by means of human A and B serums and anti-O ox serum. Data on these hereditary characters are of interest primarily in regard to their genetic linkage and will be reported in a separate article. The present paper will be concerned chiefly with the ocular findings.

Ectopia lentis, a congenital subluxation of the crystalline lens, has been the subject of intensive study since it was first described by von Graefe,[2] in 1854. This ocular anomaly is most frequently manifested as a bilateral symmetric displacement (subluxation) of the lens, but occasionally there may be great differences between the two eyes in the degree of displacement. Associated ocular defects have been reported which vary greatly in the type and mode of expression in different families. Axial and lenticular myopia, coloboma of the iris, coloboma of the iris and lens, corectopia, iridodonesis, ectopia pupillae, megalocornea, miosis, amblyopia, strabismus and persistent pupillary membrane have been most frequently reported. Ectopia lentis has also been observed as an associated anomaly in the syndrome described first by Marfan,[3] in 1896, under the name of dolichostenomelia.

Dr. Falls is Walter R. Parker Scholar in Ophthalmology, University of Michigan.

Records of all persons described in this report are on permanent file in the Heredity Clinic, University of Michigan.

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From the Department of Ophthalmology of the University Hospital and the Department of Human Heredity of the Laboratory of Vertebrate Biology, University of Michigan.

1. Landsteiner, K., and Wiener, A. S.: J. Exper. Med. **74**:309, 1941.
2. von Graefe, A.: Arch. f. Ophth. **2**:255, 1854.
3. Marfan, M. A.: Bull. et mém. Soc. méd. d. hôp. de Paris **13**:220, 1896.

This syndrome, now commonly termed arachnodactyly, is characterized by (1) elongation of the long bones (especially those of the hands and feet), (2) spinal curvature (scoliosis and kyphosis), (3) dolichocephalic skull, (4) underdeveloped musculature, (5) pes planus and hammer toes, (6) pigeon breast, (7) absence of subcutaneous fat and (8) infantilism. Achard,[4] in 1902 called attention to the associated ocular anomalies and to the fact that 40 to 60 per cent of arachnodactylous persons manifested some pathologic ocular condition: ectopia lentis, iridodonesis, nystagmus, congenital miosis, strabismus and anomalies of the lids and lashes.

Ectopia lentis is inherited as a dominant character in the vast majority of published pedigrees. This is true of the simple forms as well as of those accompanied by ocular or other defects. Minor degrees of the defect are frequently overlooked unless careful ophthalmologic examination is made, and this may account for some of the familial cases. Complete failure of expression of the gene in certain heterozygotes or occasional mutation may account for other cases of a familial or sporadic nature. True recessive inheritance of this defect is probably rare, since only 3 or 4 cases of parental consanguinity have been reported.

Judging from the genetics of other human and animal abnormalities, it is probable that several different mutations, at the same or at different chromosome loci, are responsible for the varying forms of hereditary ectopia lentis in different kindreds. The available data are too limited to permit of a precise analysis. It is our hope to make available more adequate data for the classification of this hereditary anomaly through a series of studies of several pedigrees.

A dominant gene is expected to be transmitted by an affected person to approximately 50 per cent of his or her offspring. In turn, an affected person is expected to have an affected parent. The normal siblings of involved persons will have children without the anomaly in question.

From the practical standpoint, the marked variability in the expression of some dominant genes is important, since the ophthalmologist is not always capable of distinguishing a person heterozygous for the abnormal gene. The oculist should attach a guarded prognosis to genetic advice given to afflicted persons and their offspring. It is known that unigene ocular anomalies may adopt different hereditary patterns in different families. Thus there arises the necessity for individualization of all patients supported by intensive study of their peculiar pedigrees. Satisfactory but slow progress is being made by clinics of human heredity in the study of linkage of the standard test factors with abnormalities. It is believed that such study will provide more accurate detection of the absence or presence of the abnormal gene in a subject and thus permit of more scientific advice to prospective parents.

METHOD OF INVESTIGATION

The pedigree chart (fig. 1) differs from the conventional diagram by having the children of a single union arranged vertically rather than horizontally. The sibships are numbered 1 to 58 and a particular person will be referred to by means of the sibship number followed by a number denoting his or her position (from top to bottom, corresponding to birth order) within the sibship. Thus, 18-3 and 18-4 are sisters, both with ectopia lentis, who married brothers, 20-4 and 20-8, thereby producing sibships 42 and 43, respectively. No information is available concerning the sibs of 1-1. The complete and exact order of birth of sibship 2 is open to question.

4. Achard, M. C.: Bull. et mém. Soc. méd. d. hôp de Paris **19**:834, 1902.

Our investigation started with affected sister and brother 32-3 and 32-4, who received the diagnosis of congenital dislocation of the lenses when examined at the ophthalmic clinic in 1935. This pair, therefore, must be regarded as the propositi of the kindred, and at the outset of the investigation no other members of the group were known. An interview with the parents and grandparents quickly established the dominant pattern of inheritance, and the defect was traced almost certainly to 1-1, who resided in Germany. Three children of this man immigrated to Ohio and left descendants, almost all of whom were known to reside in and about Toledo. It was then decided to examine all of these persons with care, and a complete pedigree was drafted before actual examination was undertaken. Subsequently it was discovered that 3 other members of the kindred had previously visited the University Hospital for ocular or other complaints. A complete

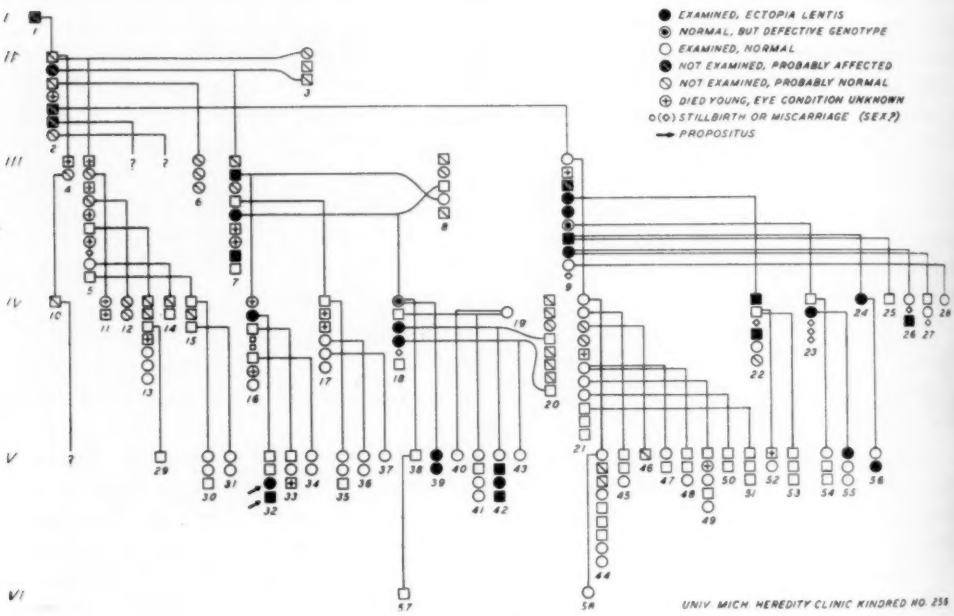

Fig. 1.—Pedigree chart.

ophthalmologic examination was performed at the University Hospital ophthalmic clinic on the following members of the pedigree: 7-2, 9-5, 9-6, 9-8, 9-8b, 13-5, 13-6, 16-2, 18-1, 21-8, 21-8a, 23-2, 24-1, 26-1, 26-3, 27-1, 27-2, 32-1, 32-2, 32-3, 32-4, 34-1, 39-1, 39-2, 50-1, 50-2, 55-1 and 56-2.

Figure 1 shows all of the known descendants of 1-1. The spouses of these descendants were examined, and none were found to exhibit signs of ectopia lentis or related defects. None of the spouses are illustrated on the pedigree chart except in 1 instance in which the wife had a child (40-1) by an earlier marriage, and in 3 instances in which double family marriages occurred, producing three pairs of double first cousin sibships, 5 and 7, 16 and 18, and 42 and 43. The last 2 combinations were produced by sibs marrying sibs, both displaying ectopia lentis. This would not be expected to alter the probability of defective children, though it might account for an increased similarity in degree of manifestation of the defect in these cousins if some of the variability in this respect was attributable to modifying genetic factors.

Genealogic information concerning the spouses was not secured except in certain cases in which we became interested in other genetic characters, such as color blindness and twinning. It is not definitely known, therefore, whether most of the unions were free from consanguinity. Where it was necessary to refer to some of the spouses this was done by attaching a letter *a* or *b* to the number of the descendant in question. Thus, 5-10*a* was the wife (not shown) of 5-10, while 9-8*b* was the second husband of 9-8 and the father of sib 27.

OCULAR ANOMALIES OF THE AFFECTED MEMBERS

Figure 2 represents the pathologic changes observed in the affected members of the kindred with the ophthalmoscope and the slit lamp when used. The pupils were not dilated in the majority of cases, and the drawings represent the lenses as seen

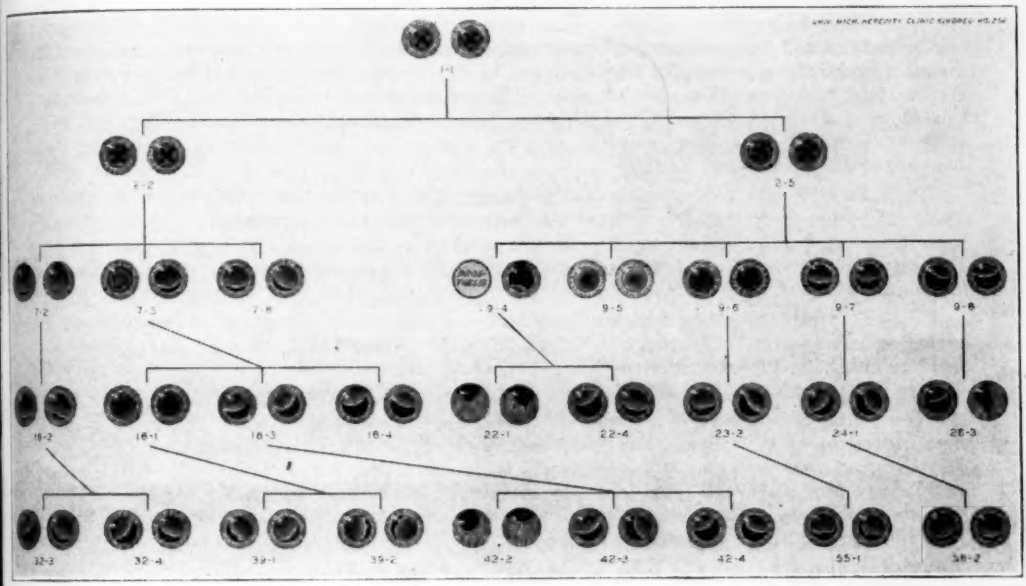

Fig. 2.—Pathologic changes observed with the ophthalmoscope and the slit lamp in the affected members of the kindred.

through the undilated pupils. A brief description of the pathologic changes and ocular anomalies for each subject follows:

1-1: This man constituted the probable ultimate source of the hereditary defect in the kindred. He resided in Germany near the city of Stolp, in Hinterpommern. Information regarding him was obtained chiefly through his grandson 7-2, as follows: "One day, after working many hours in the field in the hot sun, my grandfather plunged his face into a bucket of cold water, and shortly afterward severe pain in his eye developed. The eye became blind, but I do not know which one. This happened when he was between 40 and 50 years of age." We interpret this episode to indicate probable secondary glaucoma resulting from displacement of the lens into the anterior chamber in view of the similar experiences of his descendants. The wife of this man was described as having normal eyes. Four of his children, 2-1, 2-2, 2-3 and 2-5, immigrated to Lucas County, Ohio, but 2-3 returned to Germany with his 3 daughters and no further information concerning his descendants was available.

2-2: This woman was known always to have had poor visual acuity and had had numerous episodes of severe ocular and head pain. The vision of one eye was lost after a severe bout of such pain. We again interpret these symptoms as sequelae of dislocated lenses.

2-5: This man was always near sighted. Episodes suggesting secondary glaucoma in the right eye were experienced at the age of 70 and again at 78, at which time this eye

was removed. We were informed by Dr. R. E. Boice of Toledo, Ohio, that the left eye showed a dislocated lens at the age of 80 and that the patient was under medical treatment for glaucoma. Although he was described as being 6 feet 1 inch (185 cm.) tall, with a maximum weight of 135 pounds (61 Kg.), signs of arachnodactyly were not evident in photographs or in descriptions by his children. Unfortunately this study was not initiated until six months after the man's death, at the age of 86, in January 1942.

7-2: At the age of 60 this man submitted to surgical treatment for the relief of chronic noninflammatory glaucoma. Bilateral iridencleisis was performed, with excellent subsequent control of the intraocular tension. At the age of 67 observation revealed that in each eye the lens was dislocated minimally up and out, was maturely cataractous and displayed a minute notch, or coloboma, inferiorly. Funduscopic examination disclosed glaucomatous optic nerve atrophy in each eye. The right eye was blind, and the visual acuity in the left eye uncorrected was 3/60 and with correction was 6/30. The tension (new Schiøtz tonometer) was 12 mm. in each eye. There was 8 to 10 degrees of left divergent strabismus (Priestley-Smith).

7-5: This 60 year old woman stated that she had had cataracts as a child and that vision in the right eye was lost after an episode of severe ocular pain. On examination the right eye was found to be blind and the visual acuity of the left 1/60 uncorrected. There were marked ectasia and dense scarring of the cornea in the right eye. The right lens was irregular, shrunken, partially calcified and held in place by dense synechias. Finger tension was 4 plus in the right and normal in the left eye. The left lens was maturely cataractous and dislocated up and in, as shown in the diagram. The left fundus was normal except for mild arteriosclerosis of the retinal vessels. Fifteen degrees of right divergent strabismus was demonstrated (Hirschberg).

7-8: This 59 year old asthenic man, a farmer, had married late in life and was without issue. His eyes were straight. There was marked iridodonesis, especially of the lower half. Both lenses were dislocated up and slightly out, with an irregular, slightly notched lower border. The visual acuity was 6/9 —1 in the right and 6/21 —1 in the left eye uncorrected. No fundus disease was observed.

9-3: This man had died without issue and was described by his brothers and sisters as having had "bad eyes." No definite details could be obtained, but he was regarded on the pedigree chart as "probably affected."

9-4: This 54 year old woman had had the right eye enucleated at the age of 28; it had been blind and painful, with anterior dislocation of the lens. At the age of 47 a complete iridectomy of the left eye was performed for relief of chronic noninflammatory glaucoma. This eye displayed a large complete surgical coloboma of the iris at 12 o'clock. Conspicuous iridodonesis was observed. The lens was completely cataractous and had gravitated into the vitreous below.

9-5: This 52 year old woman had married late in life and was without issue. Her uncorrected visual acuity was 6/15 in the right eye and 6/30 in the left eye. An incipient alternating divergent strabismus of 8 to 10 degrees was present. The irises were a light gray-blue. No iridodonesis was demonstrable. Slit lamp examination revealed long attenuated zonular fibers conspicuously especially from 5 to 8 o'clock in the right and from 3 to 7 o'clock in the left eye. An occasional ruptured zonal fiber could be seen freely waving in the aqueous. Minimal, but conspicuous, lenticular nuclear sclerosis was present in both eyes. The funduscopic examination gave normal results except to show minimal arteriosclerosis of the retinal vessels and minor macular degenerative changes in both eyes. The visual fields were normal for both eyes. The patient accepted the following manifest correction:

Right eye: +0.75 D. sph. ⌒ +0.25 D. cyl., axis 98; vision, 6/4.5 —4
Left eye: +1.25 D. sph. ⌒ +0.37 D. cyl., axis 57; vision, 6/4.5 —5
Both eyes: +2.25 D. sph. for reading; for Jaeger type 1 at 31 cm.

9-6: This 50 year old woman had no ocular complaints other than those of presbyopic origin. The uncorrected visual acuity was 6/12 —2 in the right and 6/12 in the left eye. The external examination gave negative results except to show incipient alternating divergent strabismus. Funduscopic examination revealed spicules of incipient senile cataract in the inferior nasal quadrant of each lens. Moderate arteriosclerosis of the retinal vessels without retinopathy was present in both eyes. No iridodonesis was demonstrable, and meticulous slit lamp examination failed to reveal any signs of pathologic change in the lenses or zonules. Gonioscopic examination did not reveal any anomaly of the anterior chamber angles.

9-7: This 47 year old asthenic man, a farmer, exhibited 5 degrees of left divergent strabismus (Priestley-Smith). There was conspicuous iridodonesis in each eye. Both lenses were dislocated up and out, the left more markedly. A conspicuous coloboma was present in

the lower border of each lens. The vision was 6/9 —2 in the right and 6/60 in the left eye uncorrected. The fundi were normal.

9-8: This 40 year old woman exhibited 15 degrees of right divergent strabismus (Priestley-Smith). Both lenses were dislocated up and out and were immaturely cataractous. Marked iridbdonesis was present in both eyes. The vision was 5/60 in the left eye uncorrected and 6/9 —2 in both eyes with correction.

16-2: This 39 year old woman gave a history of episodes of blurred vision accompanied by haloes about lights. The intraocular tension was 26 mm. of mercury in each eye with the pupil undilated and 12 mm. with the pupil dilated (new Schiøtz tonometer). The corrected visual acuity was 6/60 in the right and 6/6 —2 in the left eye with a minor correction for compound myopic astigmatism. Prominent iridodonesis was present in both eyes. Both lenses were dislocated up and out, and each presented a small coloboma in the inferior border. The funduscopic examination revealed nothing abnormal except hypertensive retinitis in each eye, grade III (Keith-Wagener).

18-1: This 41 year old woman had visual acuity of 6/6 —3 in the right and 6/9 —4 in the left eye without correction and of 6/6 and 6/6 —1 with correction. External ocular examination revealed only a few degrees of alternating divergent strabismus. The point of basal convergence was 130 mm. There was no evidence of iridodonesis or other indication of ectopia lentis. The fundi were normal except for grade III (Keith-Wagener) hypertensive retinitis without retinopathy. A minor compound hyperopic correction was worn.

18-3: This 34 year old woman had submitted to extraction of a completely dislocated lens in the right eye and secured a satisfactory result. The vision in both eyes was 1.5/60 without correction and 6/9 —3 with correction. Iridodonesis was present in both eyes. There was a complete surgical coloboma of the right iris with incarceration of the temporal pillar. The left lens presented zonular cataractous changes and was dislocated up and out to a degree sufficient to give aphakic vision. No gross funduscopic change was observed except peripheral inactive chorioretinitis in the left eye.

22-1: This 30 year old mechanic had experienced dislocation of the right lens into the anterior chamber in September 1940. The lens was successfully extracted by Dr. J. L. Roberts, of Toledo, Ohio. The left lens became dislocated into the anterior chamber two months later, and the same surgeon secured a similar good result. The vision was 1.5/60 in both eyes uncorrected and 6/9 + 3 in the right and 6/9 —2 in the left with correction. Examination of the fundi disclosed many opacities of the vitreous but no retinal disease. A complete surgical coloboma of the iris was present superiorly, and both pupils were boat shaped.

22-4: This 22 year old man was not willing to submit to examination by us, but details were obtained from his local ophthalmologist. His vision in 1931 was 6/60 in the right and 6/30 in the left eye uncorrected and with correction 6/30 + 2 and 6/30. The lenses showed no cataractous changes but were dislocated up and out. No retinal disease had been observed at that time.

23-2: This 27 year old asthenic woman, a housewife, manifested 10 degrees of left divergent strabismus (Priestley-Smith). Her uncorrected vision was 6/21 in the right and 1/60 in the left eye. The external examination disclosed mild paresis of the right inferior oblique muscle. Complete iridodonesis was evident in both eyes. The lenses were dislocated up and out. No important funduscopic changes were present.

24-1: This 27 year old asthenic woman had uncorrected visual acuity of 6/21 in the right and 1/60 in the left eye. There was 15 degrees of left divergent strabismus. There was iridodonesis in each eye, and both lenses were dislocated up and out. Both disks were best seen with a —20 lens. A small inferior myopic temporal conus was visualized in each eye. The lower border of the right lens was deeply notched, as illustrated. The central inferior portion of the lens was pulled out into a tag by adherent zonular fibers. The picture was similar but less pronounced in the left eye.

26-3: This 19 year old youth experienced dislocation of the left lens into the anterior chamber in 1934, and extraction was attempted. Considerable vitreous was lost during the surgical procedure, with subsequent organization of the vitreous and retinal detachment. Examination revealed 10 degrees of left convergent strabismus. Paresis of the external rectus muscles was demonstrated. Iridodonesis was present in both eyes. The finger tension was subnormal in the left eye. The left cornea was scarred and exhibited band keratitis. There was a complete surgical coloboma above. The pupillary opening was filled with a dense gray membrane. No fundus details were visualized in the left eye. The right lens was dislocated up and out, the lower border of the lens crossing in the middle of the pupillary opening. No fundus disease was seen in the right eye. The slit lamp examination revealed minimal notching in the lower border of the lens, and fluid vitreous could be seen bulging into the

anterior chamber. The visual acuity was 6/30 in the right eye with a correction of + 12.50 D. sph. ⌒ + 1.75 D. cyl., axis 168.

32-3: This asthenic 17 year old girl had uncorrected vision of 2/60 in both eyes. With correction the vision was 6/9 —2 in the right and 6/12 —3 in the left eye. There was definite iridodonesis in both eyes. Both lenses were dislocated up and out, the right more markedly. The fundi were normal. The refractive error through the phakic portion of the pupil was:

Right eye: —8.00 D. sph. ⌒ — 6.00 D. cyl., axis 115; vision, 3/60
Left eye: —8.00 D. sph. ⌒ —10.00 D. cyl., axis 70; vision, 2.5/10

Through the aphakic portion of the pupil the error was:

Right eye: + 11.00 D. sph. ⌒ + 2.00 D. cyl., axis 112; vision, 6/ 9 —2
Left eye: + 10.50 D. sph. ⌒ + 2.50 D. cyl., axis 65; vision, 6/12 —3
Both eyes: + 2.50 D. sph. for reading; Jaeger type 4, right eye, and Jaeger type 1 at 26 cm., left eye

32-4: This asthenic 16 year old boy had uncorrected visual acuity of 1/60 in both eyes. External ocular examination gave negative results except to reveal iridodonesis in both eyes. Both lenses were dislocated up and out to a degree which permitted aphakic vision. The fundi were normal. The refractive error through the aphakic portion of the pupil was:

Right eye: + 13.00 D. sph. ⌒ + 0.75 D. cyl., axis 115; vision, 6/9 —1
Left eye: + 13.00 D. sph. ⌒ + 0.75 D. cyl., axis 72; vision, 6/9 —1
Both eyes: + 2.50 D. sph. for reading; Jaeger type 1 at 26 cm.

39-1: This stocky 16 year old girl had uncorrected vision of 6/12 —2 in the right and 6/9 —3 in the left eye. There was iridodonesis in both eyes. Both lenses were dislocated up and in. The fundi were normal.

39-2: This slim 14 year old girl had uncorrected visual acuity of 6/12 —3 in both eyes. The eyes were straight at times, and at other times there was a few degrees of alternating divergent strabismus. Mild paresis of the superior rectus muscles was demonstrated. There was iridodonesis in both eyes. Both lenses were dislocated down and out, with notching as illustrated. The fundi were normal except for astigmatic distortion.

42-2: This asthenic 13 year old boy was aphakic in both eyes, having submitted to surgical intervention for dislocated lenses three years before our examination. There was 8 to 10 degrees of left divergent strabismus. The left pupil was large and boat shaped, as illustrated. Incarceration of the iris pillars was present in both eyes. There was conspicuous iridodonesis in both eyes. The fundi showed marked myopic temporal conus and myopic retinal degeneration. The visual acuity was 1.5/60 in both eyes uncorrected and 6/15 —2 in the right and 6/60 in the left corrected.

42-3: This 7 year old girl had uncorrected visual acuity of 3/60 in both eyes. The eyes were straight in the primary position, but there was paresis of the superior rectus muscles. Iridodonesis was present in both eyes. The lenses were dislocated up and out, the left more laterally. Posterior subcapsular opacification was noted in both eyes. Mild myopic changes in the retina were seen in both eyes.

42-4: This stocky 4 year old boy would not cooperate sufficiently to permit an adequate impression to be gained of his visual acuity. Most of his ocular habits indicated a rather high myopic error of refraction. The eyes were straight, but there was paresis of both inferior oblique muscles. Iridodonesis was present in both eyes. Both lenses were dislocated up and out. No fundus details could be seen because of the poor cooperation; however, no cataractous changes were observed in either eye.

55-1: This stocky 6 year old girl had uncorrected visual acuity of 6/20 —1 in the right and 3/60 in the left eye. The eyes were straight at times and showed a few degrees of alternating divergent strabismus at others. There was paresis of the right superior rectus muscle. There was iridodonesis in both eyes. The left pupil was 1 mm. larger than the right. Both lenses were dislocated up and out. The fundi were normal.

56-2: This stocky 3 year old girl could not be tested for visual acuity, but gross tests with objects indicated reduced vision in both eyes. An incipient alternating divergent strabismus was present. The lenses were dislocated up and out. An associated iridodonesis was seen in both eyes. A minute coloboma of the inferior border of each lens could be seen. The funduscopic examination gave negative results.

The ectopia lentis as expressed in this pedigree is obviously produced by a dominant gene. A most interesting variability of expression is present, the degree

of lenticular dislocation running the gauntlet from gross normality to complete luxation. Two women, 18-1 and 9-6, at their present ages of 40 and 50 show no gross anomaly of the lens zonules or position. Though apparently normal, these women must certainly possess the morbid gene, since they are children of defective parents and in turn have produced defective children and grandchildren. The woman 9-5 would have been considered normal if slit lamp examination had not been performed. The theory of "lack of penetrance" of the abnormal gene affords a rather unsatisfactory genetic explanation for such variability of expression. Also, it is not known whether the gene is fully dominant to the normal allele, since homozygotes for the defective gene are not known and in the heterozygous condition there is such a variable expression of the character. It would perhaps be better to call the abnormal gene a nonrecessive. True recessive inheritance of this defect is probably very rare, since, as previously stated, only 3 or 4 cases of parental consanguinity have been reported.

OTHER ABNORMALITIES

Strabismus.—One hundred and nineteen persons were examined for gross evidence of strabismus. Among the 25 exhibiting ectopia lentis, 15, or 60 per cent, displayed some variety of strabismus; 9 had eyes which were straight in the primary position, and 1 had monocular prosthesis. Only 5, or 5.3 per cent, of the persons without ectopia lentis evidenced any gross strabismus.

Myopia.—Except in 24-1, 42-2 and 42-3, the myopia observed in the affected members was of lenticular, rather than axial, origin. Aphakic errors of refraction, such as +13.00 to +15.00 D. sph., and the absence of myopic retinal degenerative changes support this finding. It has been our experience that most of the myopia is of lenticular origin in kindreds showing ectopia lentis. Indeed, it has been so frequently observed that we have come to regard compound myopic astigmatism as one of the minor criteria by which the diagnosis of ectopia lentis can be supported when other signs are not too clear.

Corneal Horizontal Diameter.—The corneal horizontal diameter was measured in all members of this kindred and ranged from 10.0 to 12.1 mm. This is well within the range of normal variation, and there has been no association of the ectopia lentis with microcornea or megalocornea in this group.

Lenticular Coloboma.—Coloboma of the lens was noted in 16-2, 23-2, 9-7, 39-2, 39-1 and 55-1. In the last 2 the defect was not apparent on gross examination but was revealed with the slit lamp. It is probable that some other affected members would have shown this anomaly had they been subjected to slit lamp examination. It was interesting to note that the coloboma resulted in areas in which the zonular fibers were absent or broken off, the indentation of the lens being apparently produced by the fibers' elastic recoil.

Iris.—We were unable to diagnose a single case of congenital corectopia or coloboma of the iris in this kindred. The observation of the color of the iris led to the conclusion that iris pigmentation is governed by factors independent of that producing ectopia of the lens. A slight pallor of the iris or heterochromia was noted in most eyes showing ectopia of the lens. This may have been the effect of mechanical trauma to the pars retinae iridis or an actual developmental anomaly of the "iris pigment."

Miosis.—Nothing conclusive can be said concerning incomplete development of the dilator fibers of the iris in this kindred, as mydriatic drugs were employed in too few cases. The affected and nonaffected members who underwent refraction

under cycloplegia did not display any inability of the iris to dilate. No abnormality of pupillary reflex action to direct light, consensual light or accommodation was noted in any member of the family examined. Serologic tests of the blood of all members examined at the University Hospital gave negative results.

Persistent Pupillary Membranes.—Persistent pupillary remnants or membranes were a frequent finding, but they occurred with approximately equal frequency in those persons having, and in those lacking, ectopia of the lens. Approximately 20.3 per cent of the eyes examined had minor degrees of this abnormality of the iris.

Anthropometric Measurements.—None of the affected members of this kindred showed skeletal deformities of a degree sufficient to permit the diagnosis of Marfan's syndrome. Nevertheless, the possibility that the abnormality might be accompanied by less pronounced changes in the long bones prompted the inclusion of 6 anthropometric measurements in the examinations. These comprised (1) total stature, (2) span, (3) biacromial measurement, (4) length of the left hand, (5) width of the left hand and (6) length of the left middle finger. All members of the kindred were measured except the younger children. Statistical analysis of the data failed to reveal an association between any of these measurements and the defect of the lens. After adjustment for age variations, the variance between affected and unaffected like-sexed sibs was in no case significantly greater than the variance among sibs of like sex and ocular conditions. There is no suggestion so far as these measurements are concerned that ectopia lentis is related to the genetic syndrome of arachnodactyly.

Gonioscopic Findings.—Gonioscopic examination was performed on 7 of the affected members. No abnormality of the filtration angle was noted with the exception of gross irregularity in its depth. This had been anticipated in view of the lenticular dislocation and tilting. Subject 7-2 presented a narrow angle glaucoma type of filtration angle with numerous peripheral anterior synechias. His iridencleisis opening was satisfactory in each eye.

Cataracts.—In this pedigree a comparison of the nonaffected and affected persons of the same age as to the presence of cataractous changes indicates that the dislocated lens is predisposed to opacification. It is probable that the interference in the normal physiology of the dislocated lens may also result in metabolic disturbances which terminate in cataractous formation.

Glaucoma.—In this study glaucoma, either secondary to complete luxation of the lens in the anterior chamber or primary noncongestive, was a frequent sequela of ectopia lentis. Anterior chamber luxation is thought or is known to have occurred in 1-1, 2-2, 2-5, 7-5, 9-4, 18-3, 22-1, 22-3 and 42-2. Primary noncongestive glaucoma had been diagnosed and surgically controlled in 7-2. Glaucomatous symptoms had been experienced by 16-2 and 18-2. No member of the pedigree who was normal so far as ectopia lentis is concerned displayed any evidence of glaucoma despite a constant search for the disease. All affected members of this pedigree were warned of the possibility of glaucoma occurring and of its serious sequelae.

TREATMENT

The treatment of ectopia lentis is preferably prophylactic. All affected persons should be made acquainted with the genetic pattern of inheritance of the anomaly and impressed with the consequences of having children. All offspring of affected persons should be subjected to a most complete ocular examination by a competent ophthalmologist in order to rule in or out the presence of ectopia lentis. When the anomaly is found, refraction with or without cycloplegia should be attempted to

secure the most satisfactory visual acuity through either the phakic or the aphakic portion of the pupillary opening. Refractive correction should be prescribed as early in life as possible in an attempt to prevent the development of amblyopia and accommodative divergent strabismus.

Ectopia lentis is not often a surgical problem unless the visual acuity is extremely poor or luxation of the lens into the anterior chamber occurs. The latter complication occurs most frequently shortly after the patient retires, when the room is dark and he is in a supine position. We have routinely suggested that physostigmine salicylate ointment (0.25 per cent) be instilled into the conjunctival cul-de-sac when the patient retires in an attempt to prevent this serious complication.

The patient with ectopia lentis with the lens in the anterior chamber presents a most serious surgical problem. Miotics are employed intensively in an attempt to constrict the pupil behind the lens preliminary to extraction. The patient is kept in a supine position on a Bradford frame during the administration of the miotic. When satisfactory miosis is secured the patient is placed prone on the usual cataract stretcher, and a corneoscleral suture is inserted. The lens is then fixated with a knife needle, and while the assistant steadies this the surgeon makes a scratch incision with a keratome or a von Graefe knife, since the anterior chamber is too shallow to permit the making of a regular corneal incision. After very slow decompression of the anterior chamber the incision is enlarged with Stevens' scissors. No iridectomy is performed. The lens is delivered with either a lens loop or an intracapsular forceps, according to which will prove more efficacious.

When the visual acuity is so poor that surgical intervention is indicated a great deal of individualization must be practiced. The position, character and extent of the lenticular displacement will determine the surgical approach. Optical iridectomy frequently gives a clear and sufficient opening for aphakic vision. In the case of nasal and inferior displacement of the lens, a carefully placed naso-inferior iridectomy may permit utilization of phakic vision. Discission of a partially dislocated lens results in a high percentage of undesirable sequelae. A discission with two knife needles followed by linear extraction when needed is suggested. The knife needles are inserted into the cornea at opposite meridians, one to fix and hold the lens and the other to rend the capsule and cortex. It is to be emphasized, however, that discission performed in this manner requires considerable experience and is not an easy procedure.

Intracapsular extraction is fraught with danger, as a large number of the eyes present fluid vitreous. Removal of the lens by loop extraction is practically always followed by serious loss of vitreous.

Glaucoma is a frequent complication of ectopia lentis. The treatment of this must also be individualized. It is our policy to treat the eye as aphakic, and, of course, the operative procedure of choice is cyclodialysis.

To summarize, surgical intervention in the treatment of ectopia lentis is a serious and dangerous undertaking.

ECONOMIC CONSIDERATIONS

Visiting the homes of the various families gave us an unusual opportunity to witness the influence of ectopia lentis on the economic status, mental and physical well-being and range of education of the affected members.

Generally speaking, the level of intelligence was average in this kindred, with no exceptional variations noted in any sibship. The homes of most were moderate to poor, being characteristic of the lower income brackets. On the whole, the kindred was composed of pleasant personalities who enjoyed pleasing marital

congeniality. The homes of the affected persons were distinctly inferior to those of their normal sibs with the exception of the farmers. It was apparent that affected persons were limited in their choice of spouses.

No exceptional educational achievement was evidenced by any of the kindred, and most of the affected members had left school early because of their ocular handicap. The lack of education was reflected in the type of vocation followed by the members with ectopia lentis.

The mental and physical well-being is greatly influenced by the presence of ectopia lentis. The affected person is impressed early in life with the fact that he is in some manner "different" from his playmates. Childhood indifference and frankness emphasize this variation. The lowered visual acuity limits the child in competitive sports and activities. Competition in the present school system is great, and a prerequisite to success is good visual acuity, which, of course, the majority of the affected persons do not possess. Thus, the child gradually falls behind his acquaintances and loses interest and self confidence, and he leaves school at the first opportunity. Ocular pain and headache are the most frequent complications and possibly accompany episodes of increased intraocular pressure. The pain described by some persons was so excruciating as to incapacitate them. The ever present threat of dislocation of the anterior chamber with subsequent glaucoma was known to most of the affected members, who limited vigorous activity in accordance.

A kindred of this character frequently becomes a burden to county and welfare funds. This family is no exception. Members 18-3 and 18-4 once were wards of the Toledo School for the Blind; 42-2, 42-3 and 42-4 had frequently been the recipients of county medical attention; 42-2 had two surgical interventions and, of course, had to be hospitalized; 24-1 and 23-2 also received county medical attention for their visual anomaly.

Many of the affected members, both in financial and in personal care, had been a great burden to their parents and relatives; 32-3, 32-4, 7-2, 9-4 and 22-1 had all been frequent visitors to ophthalmic clinics and ophthalmologists, at no mean expense to their supporters; 7-2 was largely dependent on his wife and daughter for his support; 26-3, with one eye useless and the other amblyopic, was an economic liability to his parents; 7-8 and 9-7 were successful farmers, possibly because farming does not place such a premium on good visual acuity.

SUMMARY

A pedigree of ectopia lentis is presented which displays dominant inheritance of the anomaly, with 2 instances of "lack of penetrance" of the abnormal gene.

No conspicuous associated anomalies of the iris, cornea or pupil were observed.

Cataractous changes are common sequelae of the dislocation of the lenses.

Chronic noninflammatory glaucoma and secondary glaucoma are frequently observed, and both carry a serious prognosis for preservation of the visual acuity.

Anthropometric measurements taken on all members of this kindred failed to indicate any association between ectopia lentis and the length of the extremities, such as is found in the syndrome of arachnodactyly.

Ectopia lentis to a considerable degree adversely affects the physical and mental well-being, the educational achievement and the economic status of the affected person.

Eugenic advice is of importance to both the unaffected and the affected members of a kindred exhibiting this dominant pathologic inheritance.

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ELECTROPHORETIC STUDIES ON SERUMS OF PATIENTS WITH OCULAR DISTURBANCES

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CHICAGO

The electrophoretic technic of Tiselius [1] has been used by a number of workers to study the proteins in normal and in pathologic human serums.[2] In this method, a boundary is formed in a specially designed U tube between a solution of proteins in a buffer and an ultrafiltrate of the solution. The application of a potential gradient across the boundary causes the original single boundary to separate into a series of boundaries corresponding to the number of electrophoretically discrete protein fractions present in the original mixture (certain anomalous boundaries being excluded). The boundaries move toward the electrode of the sign opposite the charge on the proteins forming the boundaries. By use of a lens system developed by Philpot,[3] and later modified by Svensson,[4] the positions of the boundaries can be visualized and the concentrations of the protein components determined. In short, the components of a mixture of proteins are separated by their difference in mobility and the number and concentrations of the components determined.

The results obtained by Tiselius [5] on horse serum, as modified by the later work of Longsworth and MacInnes,[6] indicated that there are four components. Stenhagen,[7] extending the work to human serums, found the same number of electrophoretically discrete fractions. The component occurring in the greatest concentration in the serum and possessing the greatest mobility has been shown to be albumin. The three remaining fractions are globulins and have been termed alpha, beta and gamma globulins. Moore and Lynn [2c] made a statistical analysis of the concentrations of the various components of the protein of normal serums. Their results show that the concentrations of the four components are remarkably constant.

Longsworth, Shedlovsky and MacInnes,[2b] in a study of the serums of 10 patients with various pathologic conditions, found notable changes in the electrophoretic components. Gutman and his co-workers [2d] reported on extensive studies

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1. Tiselius, A.: Tr. Farad. Soc. **33**:524, 1937.

2. (*a*) Blix, G.: Ztschr. f. d. ges. exper. Med. **105**:599, 1939. (*b*) Longsworth, L. G.; Shedlovsky, T., and MacInnes, D. A.: J. Exper. Med. **70**:399, 1939. (*c*) Moore, D. D., and Lynn, J.: J. Biol. Chem. **141**:819, 1941. (*d*) Gutman, A. B.; Moore, D. H.; Gutman, E. B.; McLellan, V., and Kabat, E. A.: J. Clin. Investigation **20**:769, 1941.

3. Philpot, J. St. L.: Nature, London **141**:283, 1938.

4. Svensson, H.: Kolloid-Ztschr. **87**:181, 1939.

5. Tiselius, A.: Biochem. J. **31**:1464, 1937.

6. Longsworth, L. G., and MacInnes, D. A.: J. Am. Chem. Soc. **62**:705, 1940.

7. Stenhagen, E.: Biochem. J. **32**:714, 1938.

made on the serums of patients with myeloma. Seibert [8] described changes occurring in the serum protein in association with tuberculosis.

The investigations of Tiselius [5] on horse serum, of Newell and co-workers [9] on allergic human serums and of van der Scheer, Wyckoff and Clarke [10] on antibacterial serums indicate that a great number of antibodies are associated with the gamma globulin fraction or with a fraction (T) with a mobility between that of the beta and that of the gamma fraction.

The investigation of the serum proteins of patients with various ocular conditions was undertaken to determine whether the local pathologic process in the eye has a widespread effect on the body fluids. The involvement of the uveal pigment and the lens, which have been shown to be antigenic [11] in various ocular disturbances, suggested that sensitization might occur and result in changes in the serum protein.

Studies of serum proteins in cases of glaucoma by earlier methods [12] failed to disclose abnormalities. However, the work of Cohn and his co-workers [13] and Gutman and his group [2d] on the comparative merits of salting-out technics and electrophoretic separation showed that the chemical method used in the earlier work is largely inadequate for determination of changes in the various fractions of the serum protein.

METHOD

Blood was drawn into a test tube, and after it had clotted the serum was poured off and centrifuged. The serum was diluted with 3 volumes of a buffer solution consisting of 0.025 molar lithium diethylbarbiturate, 0.025 molar diethylbarbituric acid and 0.025 molar lithium chloride, described by Longsworth, Shedlovsky and MacInnes.[2b] The buffer has a p_H of about 7.8 at 25 C. The p_H, which was determined for each specimen with the glass electrode, was 7.8 ± 0.1 for all serums. The diluted serum was dialyzed against 2 liters of buffer for at least forty-eight hours in the ice box, with merthiolate as a preservative. After being filtered, the dialyzed serum was placed in the electrophoresis cell in the usual manner and the separation carried out. Photographs of diagrams of the boundaries obtained with the Philpot-Svensson lens system were made, and the descending pattern was enlarged for determination of the areas under the peaks. The concentrations of the various fractions were obtained from the descending areas. The total protein concentration of the serum was determined by the falling drop method.

RESULTS

The data obtained in the electrophoretic analyses of the serums of 18 patients with various pathologic ocular conditions are presented in the table. For comparison, the statistical values of Moore and Lynn [2c] for normal serums are also given. Results of analyses of normal serums in the laboratory with which we are associated are in complete agreement with these values.

Before the changes in concentration of the serum protein fractions are considered, it must be pointed out that the patients used in this study for the most part had other pathologic conditions associated with the ocular lesions; these complicating states might be responsible for the changes observed or might mask

8. Seibert, F. B.: J. Biol. Chem. **143**:29, 1942.

9. Newell, J. M.; Sterling, A.; Oxman, M. F.; Burden, S. S., and Kreja: J. Allergy **10**:513, 1939.

10. van der Scheer, J.; Wyckoff, R. W. G., and Clarke, F. H.: J. Immunol. **39**:65, 1940.

11. (*a*) Uhlenhuth, in Festschrift zum sechzigsten Geburtstage von Robert Koch, Jena, G. Fischer, 1903. (*b*) Römer, P.: Arch. Ophth. **60**:175 and 239, 1905. (*c*) Elschnig, A.: Arch. f. Ophth. **75**:459, 1910; **76**:509, 1910. (*d*) Elschnig, A., and Salus, R.: ibid. **79**:428, 1911. (*e*) Wood, A. C.: Arch. Ophth. **45**:557, 1916; **46**:8, 283 and 503, 1917; **47**:161 and 181, 1918; Tr. Ophth. Soc. U. Kingdom **45**(1):208, 1925.

12. Römer.[11b] Elschnig.[11c]

13. Cohn, E. J.; McMeekin, T. L.; Oncley, J. L.; Newell, J. M., and Hughes, W. L.: J. Am. Chem. Soc. **62**:3386, 1940.

Data Obtained in Electrophoretic Analyses of the Serum of the Eighteen Patients with Ocular Diseases

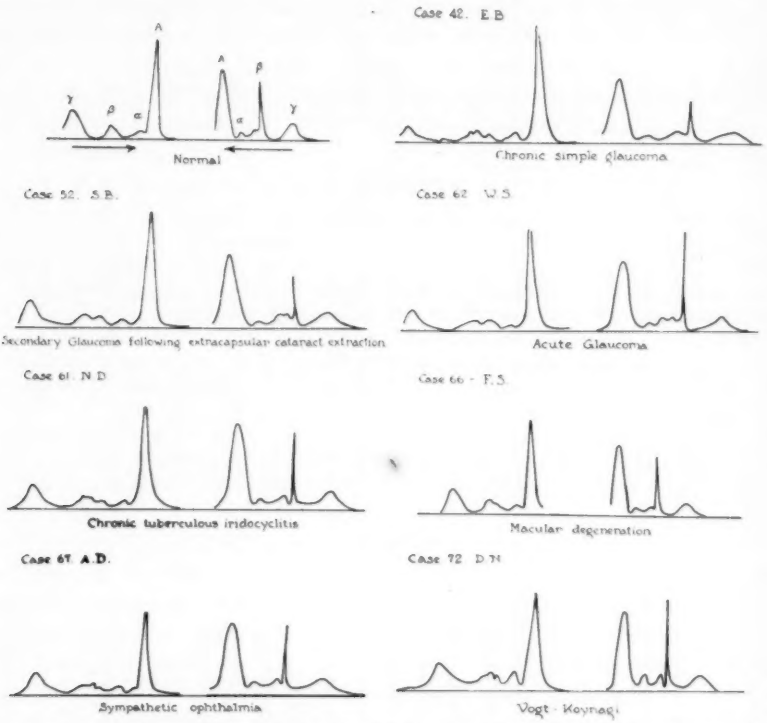
Patient	Ocular Condition	Case No.	Albumin / Globulin	α-Globulin / Albumin	β-Globulin / Albumin	γ-Globulin / Albumin	Total Protein*	Albumin*	Globulin*	α Fraction*	β Fraction*	γ Fraction*
J. G.	Chronic simple glaucoma	39	1.42	0.10	0.33	0.28	6.65	3.90	2.75	0.37	1.29	1.09
W. L.	Chronic simple glaucoma	40	1.23	0.19	0.26	0.36	6.05	3.34	2.71	0.64	0.87	1.21
E. B.	Chronic simple glaucoma	42	1.49	0.13	0.36	0.21	6.47	3.88	2.59	0.51	0.81	1.41
E. N.	Chronic simple glaucoma	43	1.41	0.12	0.35	0.24	5.92	3.46	2.46	0.37	1.24	0.83
R. B.	Chronic simple glaucoma	45	1.29	0.15	0.30	0.33	5.81	3.28	2.53	0.49	0.97	1.08
W. B.	Chronic simple glaucoma	76	1.03	0.17	0.48	0.32	6.99	3.55	3.44	0.60	1.70	1.13
A. W.	Chronic simple glaucoma	75	1.22	0.11	0.38	0.30						
S. B.	Secondary glaucoma	52	1.58	0.11	0.30	0.22	6.54	4.01	2.53	0.44	1.20	0.88
H. R.	Secondary glaucoma	54	1.06	0.17	0.29	0.47	7.20	3.70	3.50	0.63	1.07	1.74
R. Mc.	Acute glaucoma	53	1.12	0.23	0.27	0.39	7.20	3.80	3.40	0.87	1.03	1.48
W. S.	Acute glaucoma	62	1.26	0.07	0.46	0.26	6.43	3.58	2.85	0.25	1.65	0.93
M. M.	Acute glaucoma	71	1.17	0.20	0.35	0.30	6.60	3.56	3.04	0.71	1.24	1.07
F. S.	Chronic iridocyclitis	47	1.41	0.23	0.25	0.22	6.70	3.92	2.78	0.80	0.98	0.86
N. D.	Chronic iridocyclitis	61	1.98	0.08	0.21	0.21	6.40	4.25	2.15	0.34	0.89	0.89
D. N.	Vogt-Koynagi disease	72	1.10	0.21	0.33	0.57	7.67	4.02	3.65	0.84	1.33	1.49
M. C.	Cortical cataract	65	1.18	0.20	0.27	0.37	6.46	3.48	3.00	0.65	0.94	1.29
A. D.	Sympathetic ophthalmia	67	1.20	0.12	0.35	0.36	6.04	3.29	2.75	0.39	1.25	1.28
F. S.	Macular degeneration	66	1.84	0.08	0.23	0.24	6.20	4.02	2.18	0.32	0.92	0.96
Normal serum			1.99	0.12	0.21	0.19	7.00	4.67	2.33	0.56	0.98	0.87
Standard deviation			±0.3	±0.025	±0.04	±0.04						

* Values are expressed in grams per hundred cubic centimeters.

more specific changes. An attempt was made to select patients with uncomplicated ocular disease, but with conditions such as glaucoma the absence of other pathologic processes is rare.

Consideration of the data in the table shows that significant changes were found in all the patients studied except for 1 with chronic iridocyclitis (case 61) and another with macular degeneration (case 66). Changes occurred in all the fractions, with no apparent correlation between the alteration in any fraction or fractions and the type of pathologic process present.

A more startling change was found in the diagrams of the ascending boundaries of serums of all the patients except the one with macular degeneration (case 66). Typical diagrams of ascending and descending boundaries found with the various



Diagrams of ascending and descending boundaries for the serums of patients with various ocular diseases and for normal serum.

pathologic conditions are presented in the figure, with the patterns of normal serum for comparison.

In all of the ascending patterns the beta boundary is composed of two or more fractions. In the pattern for chronic simple glaucoma there are three peaks at the position of the beta boundary, and an additional boundary appears between the beta and the gamma fraction. In the patterns for secondary glaucoma and acute glaucoma, the beta boundary on the ascending side is clearly separated into two fractions, and the boundary on the descending side also shows a splitting of this fraction. The ascending patterns for serums of patients with other pathologic conditions show the new boundaries to varying extents. It is noteworthy that the serum of the patient (case 61) with chronic iridocyclitis, which gave normal protein concentrations, clearly shows the changes in the beta boundary.

COMMENT

Ocular disease cannot definitely be held responsible for the significant changes in the concentrations of the protein fractions in the serum of the patients studied because of the existence of other pathologic conditions which might complicate the picture. However, the appearance of new fractions in the beta boundary may be assigned to the ocular lesion with more certainty because of the failure of other investigators to find these changes associated with a large number of other pathologic conditions. The appearance of new protein fractions seems to be a characteristic observation in cases of chronic intraocular disease.

It is possible that this alteration in the serum protein picture is caused by the elaboration of a new fraction by the body in response to some antigen originating in the eye. In all probability, this antigen is either uveal pigment or lens protein, since these substances are the only homologous antigens which have been demonstrated in the eye. The appearance of the new fraction with conditions in which the lens is thought not to be involved suggests that the pigment is the more important factor.

The reason for the absence of the new boundary or boundaries on the descending side of the diagram of a number of serums is not known. Its presence on the descending side in certain of the serums indicates that the change might appear in all diagrams on more prolonged electrophoresis, but the possibility that this alteration is due to the breaking of some complex in the beta boundary must be considered.

Further work on the entire problem is in progress.

SUMMARY

Electrophoretic analyses of the serums of patients with various ocular diseases have been made.

Significant changes in the concentration of the electrophoretic fractions have been found. These changes did not appear to be characteristic of any given ocular condition.

A new boundary with a mobility between that of alpha and that of beta globulin appeared in the ascending pattern of serums of patients with chronic glaucoma, iridocyclitis and sympathetic ophthalmia.

Slight indications of the new fraction in the serum of patients with secondary glaucoma following extracapsular extraction and cortical cataract were found.

The possible relation of the changes in the protein of the serum to sensitization is discussed.

The electrophoretic equipment used in this study was constructed with funds furnished by the Abbott Research Foundation of Northwestern University and the American Association for the Advancement of Science.

Dr. S. R. Gifford gave advice and aid in this study.

Northwestern University Medical School.

A NEW OPHTHALMIC IMPRESSION MATERIAL

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The satisfactory fitting of contact lenses became a possibility when J. Dallos, in 1933, discovered the feasibility of making molds of the living human eye with Pollner's negocoll.

The disadvantages of the use of negocoll involve primarily physical factors, such as the time consumed in preparation. The boiling for liquefaction takes almost an hour. The hot liquid negocoll must be transported in a thermos jar and subsequently cooled in a glass beaker. With constant agitation with a stirring thermometer, it is cooled to an exact temperature, at which it must be immediately placed on the eye. The slight chemosis produced by the heat of the liquid negocoll (106 F.) and the slight sting experienced by the patient after the mold has been removed, while not of much consequence, are also undesirable.

One of my students, who has made a hobby of contact lenses, observed a technic for the molding of living tissues other than the eye. This drew his attention to a preparation which he believed would be superior to negocoll. He sent an experimental quantity of this material to me and to Mrs. Gertrud Salvatori, who has made several thousand contact molds. She immediately began clinical experimentation. During the early months of her work, facts were uncovered which necessitated changes in the formula of the molding material as originally submitted. With the cooperation of the manufacturing chemists, the present formula of the new molding powder was attained in the summer of 1942.

As soon as the basic experimental work was completed, the finished product was demonstrated to me. I immediately verified the observations of Mrs. Salvatori and have used the new molding powder for six months.

After 500 clinical patients had been observed and studied under medical supervision, the new molding preparation was released for general use under the name moldite powder.[1] It is an alginate gelling agent which reacts when mixed with distilled water. The gelling is retarded by a preparation which gives sufficient time for the material to be placed on the eye and the molding shell centered before the gelling takes place.

The advantages of moldite powder over negocoll may be stated as follows:

1. Heating utensils, thermometer, thermos bottle and beakers are eliminated.

2. The preparation is simple; the powder is merely mixed with distilled water and the mixture spatulated for two minutes.

3. The setting time can be regulated by variation of the temperature of the water and the time of spatulation. Warm water causes more rapid gelling; cold water retards gelling.

4. This material remains in a flowing state for about four minutes from the time it is first mixed with distilled water at room temperature. This latent period, before actual gelling, is valuable in that it gives the eye time to become fixed in

1. This is a product of secret composition; according to the author, the manufacturer refuses to provide the formula for it.

a state of rest and also allows any alteration of the position of the casting shell without the production of conjunctival wrinkling.

5. The gelling process starts abruptly and continues rapidly to completion in about thirty seconds. In cases of nystagmus this feature is important.

6. When the casting shell is removed, it is immediately evident that the moldite separates very readily from the eye and that manipulation of the upper lid is not necessary.

7. The elasticity of the preparation is such that particles of the gel seldom break off and remain in the fornices. This eliminates any manipulation by instrument or other means to remove foreign bodies. A simple irrigation is sufficient.

8. After the casting is completed, the eye appears normal, with slight signs of irritation, as evidenced by the absence of conjunctival injection, chemosis, tearing and photophobia.

9. The patient does not complain of burning, stinging or other disagreeable symptoms.

10. There is no greater blurring of vision or alteration of visual acuity than would be experienced from a similar instillation of local anesthetic and epinephrine

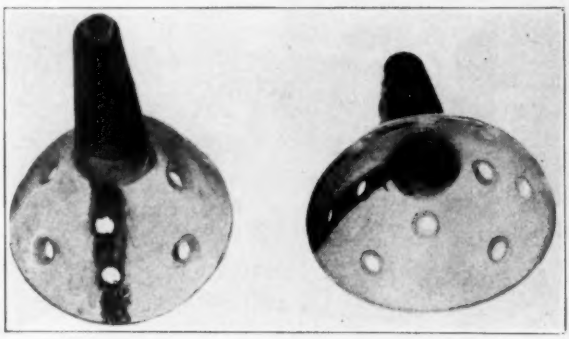

Fig. 1.—Perforated plastic casting shells.

without the molding. The slight blur which is occasionally experienced disappears in half an hour.

TECHNIC

The technic of making a mold of the human eye in moldite is simple and rapid. The equipment necessary consists of: two rubber bowls (one for the moldite and one for the dental stone); one spatula; two casting shells; one wide-mouthed 10 cc. graduate; one cylinder 10 cc. graduate; moldite powder; dental stone (castite is best); distilled water, and a muscle hook.[2]

For a rapid, successful molding, the patient should be prepared both physically and mentally in order to insure his active cooperation.

To quiet his imagination, the entire procedure should be described briefly. The only instrument to be used near his eyes, the muscle hook, should be shown him with the comment that it is nothing but a bent piece of well rounded wire, with no sharp edges. As trial contact lenses have already been applied, he should be told that the molding is no more disagreeable than the insertion of these lenses.

It should be forcefully stated that the successful completion of the molding depends on his cooperation, principally in four ways: First, he must keep the eye not being worked on open and gazing at a predetermined point in order to center the cornea properly; second, he must keep his eyes quiet and fixed on this point for the second two minutes at least;

2. The equipment described in this article can be obtained from the Obrig Laboratories, Inc., 49 East Fifty-First Street, New York.

third, he must move his eyes as he is directed when the mold is being removed, and, fourth, he must keep his eyes wide open at all times and must not squeeze his lids down at any time during the process. Actually, all this is simple, and it is seldom that a patient gives any trouble. If he squeezes down the lids, the operator should stop work until he relaxes them again. No harm can come if the moldite and the casting shell on the eye are left for a short time. The operator should take his time and work deliberately and according to routine.

The casting shell which I use at present is the product of a gradual modification of the original glass molding shell designed seven years ago. Within the year important changes have been made which add considerably to its efficiency. The present solution of the problem is a plastic molding shell 24 by 27 mm. It has much the shape of an eye cup, with the flat base removed. The depth of the shell from the shallowest portion of the arched edge to the integral hollow handle is approximately 10 mm. The handle is 25 mm. long, slightly tapered, completely hollow and open at the end. The shell wall is pierced with multiple perforations about 1 mm. in diameter. These perforations, in conjunction with the hollow handle, allow the excess moldite gel to escape as the shell is placed on the eye, any pressure

Fig. 2.—Simplified equipment for the making of molds of the eye with moldite.

on the eyeball being thus eliminated. The perforations further prevent the loosening and separation of the moldite from the casting shell during its removal from the eye by affording it firm anchorage.

One of the long ends and the handle of the shell are marked with a red line to indicate the position of the right nasal side (red for right). Green markings are placed on the shell used for the left eye.

The patient should have thorough anesthetization of the conjunctiva and cornea with a 0.5 per cent solution of pontocaine hydrochloride. Two drops of the anesthetic is placed in each eye five minutes before the moldite powder is mixed. Two minutes should elapse before the second drop is instilled. A third drop may be instilled in the eye for which the cast is to be made when spatulation is begun. A minute later a fourth drop of anesthetic and 1 drop of epinephrine hydrochloride (1:1,000) are instilled.

The patient is placed in a supine position in a treatment chair or on a table, the operator making sure that the head is in a comfortable position; the procedure is then as follows:

1. Ten cubic centimeters of moldite powder is measured out in the wide-mouthed graduate and 7 cc. of distilled water in the cylinder graduate. The powder and water are mixed in a small rubber bowl and spatulated to a smooth creamy mixture, about the consistency of face cream, the process being continued for two minutes.

2. The patient is instructed to fix his gaze so that the eye for which the cast is first to be made (usually the right) is turned so that the lower edge of the iris is at the level of the lower lid down and slightly to the nasal side. The upper and temporal scleral areas are the most important in a good mold.

3. The operator should work from back of the patient's head rather than from the side.

4. The assistant should dry both lids.

5. The moldite is scooped up on the spatula and the mixture placed in the casting shell.

6. The casting shell is held concave side up in the right hand, with the line marking the inner canthus facing toward the outer canthus, so that when the shell is turned over to be placed on the eye the mark will be directed nasally.

7. The upper lid is seized with the index finger of the left hand, the finger being parallel with, not at 90 degrees to, the margin of the lid. This gives better traction. The lid is retracted as far back as possible. The assistant retracts the lower lid at the same time, with a piece of gauze over his finger to insure traction.

8. The casting shell with the moldite is turned over and placed under the upper lid with the canthus mark turned up in the right eye and down in the left eye. Pressure is exerted against the upper lid, contact with the cornea being avoided. The whole shell is then rotated clockwise, so that the marking line is turned to the inner canthus and the shell slipped down under the lower lid. If the operator misses getting the shell under the upper lid, he should not work where the spilled moldite keeps him from seeing what he is doing. The shell should be removed, the moldite allowed to set, the material removed, the eye washed out and the process started over again. If the lower lid does not slip over the casting shell at first, the assistant should push up on the handle of the casting shell and retract the lower lid once more with a piece of gauze over his finger to give traction.

9. As soon as the casting shell is on the eye, the lids are released. The handle of the shell should not be held. The assistant may run his fingers up over the edge of the lower lid to make sure that it is over the casting shell. The margin of the lid cannot be seen because of the overflowing moldite.

10. The excess moldite should not be wiped away. As much as possible is spilled on the lids and lashes. It acts as a splint.

11. The patient must keep the free eye wide open and steady, without blinking if possible. This should be comparatively easy because of the anesthesia. No reflex due to drying of the cornea is likely to occur.

12. Five minutes from the time the powder and water are mixed the moldite will gel on the eye. The gel on the outside of the eye is then removed. First, the lashes of the upper lid are pulled out of the moldite with the muscle hook. Then the edges of the moldite gel are loosened from the lids, the cheek and the region of the inner canthus. If the entire mass is carefully worked and raised with the index finger and the hook, it will all come off in one piece. The operator should not be concerned, however, if it must be removed in a number of pieces. He should take his time; no discomfort is given the patient.

13. The patient is instructed to look up toward the operator as far as possible. The lower lid is retracted with the index or the second finger of the left hand. Firm pressure is directed upward on the handle of the casting shell with the thumb or the index finger of the same hand, and it is forced gently toward the eyebrow. With the muscle hook in the right hand, the operator gently stretches the folds of the bulbar conjunctiva downward and away from the casting shell with the portion of the hook forming the rounded angle. At the same time slight pressure is exerted on the sclera until air is heard or felt to enter under the casting.

14. The patient is instructed to look down and the casting shell is removed, slight pressure being maintained against the upper lid as the shell is pulled down and out.

15. The moldite mold is filled at once with fixing solution. This is important. The casting shell is placed, handle down, into a short, squat, narrow-mouthed bottle, such as that in which opticians obtain spectacle screws. The fixing solution is prepared from the white tablets supplied with the moldite powder. One tablet is dissolved in 200 cc. of water. The fixing solution should be kept in a conspicuously marked bottle, so that it will not be confused with the distilled water or come in contact with the eye.

16. The attending physician should now irrigate the eye thoroughly to remove any small particles which may have become detached from the outside of the casting shell.

17. The cast is made for the left eye with the same technic except that no anesthetic is instilled into the right eye. Two instillations into the left eye of the anesthetic and one of the epinephrine solution is all that is necessary.

18. With both negative molds completed and filled with fixing solution, about ½ inch (1.27 cm.) of water is poured into the second rubber bowl and sufficient castite (hard dental stone) sprinkled on with the spatula to absorb all the water, and then a bit more is added. This mixture is spatulated well. The bowl is tapped to force any air bubbles to the surface. The dental stone is mixed as thick as possible, but thin enough that it will flow.

19. The fixing solution is poured out of the negative mold and the mold dried lightly with a piece of cotton.

20. The dental stone is poured into the negative mold from the side, without contact with the moldite gel or the casting shell. One can do this by pressing the rubber bowl into a spout and alternately pressing on and releasing the spout, so that the stone is forced into the mold. If castite is used, it will level off with no attention.

21. The stone is allowed to harden for about a half-hour.

22. With a stylus or a pencil with a sharp point, a horizontal line is drawn from the inner to the outer canthus. The operator holds the casting as if he had just removed it from his own eye, with the inner canthus mark directed toward his own inner canthus. Then, above the horizontal line, in the center, an *R* is engraved for the right eye and an *L* for the left eye; an *N* is engraved to the nasal side, and a *T* to the temporal side. Below the line the patient's name is engraved, thus:

TLN	NRT
Jones	Jones

23. In about an hour the positive cast is separated from the negative mold. If castite stone is used, this is easy.

49 East Fifty-First Street.

EFFECT OF SULFONAMIDE OINTMENT ON HEALING OF EXPERIMENTAL WOUNDS OF RABBIT CORNEA

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The local treatment of various infective processes of the eye with sulfonamide compounds has been reported, but the results obtained have not been uniform.[1] According to Bellows,[1c] topical application of sulfonamide compounds is "effective in pyogenic dermatoses, infectious blepharitis, inclusion blennorrhea, and some forms of acute conjunctivitis." These substances also have been used locally in prophylactic treatment and in therapy of open surgical wounds subject to contamination with micro-organisms.[2] According to Long [3] "sulfonamide ointments are of value in the treatment of infected wounds." The local application of crystalline sulfonamide compounds has been recommended for the treatment of war wounds, in which infections with gas bacilli, staphylococci or hemolytic streptococci are likely to occur.[4] Recently, the use of sulfanilamide and its derivatives, either in the form of powders or incorporated in ointments, has been suggested for the treatment of fractures of the orbital walls and of burns of the eyelids or the anterior portion of the eyeball.[5]

Experimental studies with sulfonamide compounds on the eyes of rabbits were first made by Rambo.[6] He showed that these compounds can be safely used in the conjunctival sac as a saturated aqueous solution, as a very fine powder or as a

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1. (*a*) Glover, L. P.: Some Uses of Sulfanilamide in Ophthalmology, Am. J. Ophth. **22**:180-184 (Feb.) 1939. (*b*) Connell, E. S., and Trowbridge, B. C.: Local Use of Sulfanilamide and Derivatives in Practice of Ophthalmology, Arch. Ophth. **27**:705-706 (April) 1942. (*c*) Bellows, J. G.: Chemotherapy in Ophthalmology, Tr. Am. Acad. Ophth. **47**:19-33 (Sept.-Oct.) 1942.

2. Key, J. A.; Frankel, C. J., and Burford, T. H.: The Local Use of Sulfanilamide in Various Tissues, J. Bone & Joint Surg. **32**:952-958 (Oct.) 1940. Kling, A. C.: Treatment of Open Wounds by the Sulphanilamide Pack, Brit. M. J. **1**:231-233 (Feb. 15) 1941. Key, J. A.: The Use of Sulfanilamide and Sulfathiazole in Orthopedic Surgery, J. A. M. A. **117**:409-412 (Aug. 9) 1941. Connell, E. S., and Trowbridge, B. C.: Local Use of Sulfanilamide and Its Derivatives in the Ear, Nose and Throat, Arch. Otolaryng. **35**:740-744 (May) 1942.

3. Long, P. H.: Sulfonamide Compounds in the Prevention and Treatment of Wound Infection: A Consideration of the Principles Which Govern Their Use, J. A. M. A. **121**: 303-307 (Jan. 30) 1943.

4. Chemotherapy in Infectious Diseases and Other Infections, War Department, Circular Letter no. 17, Washington, D. C., Government Printing Office, 1942. Keefer, C. S.: Hemolytic Streptococcal Infections in Wartime, South. M. J. **35**:143-146 (Feb.) 1942.

5. Berens, C., and Hartmann, E.: War Injuries of the Eyes, J. M. Soc. County of New York **1**:5-7 (Aug. 15) 1942.

6. Rambo, V. C.: The Effects of Sulfanilamide as Determined in the Eyes of Rabbits, Am. J. Ophth. **21**:739-746 (July) 1938.

5 per cent suspension in olive oil. Injection of 0.02 Gm. of sulfanilamide in aqueous suspension into 4 eyes infected with streptococci resulted in complete healing of 3 eyes and in a delay of the infectious process in the fourth, while 4 untreated control eyes became purulent within four days. Sulfanilamide applied in ointment form readily penetrated the normal cornea of the rabbit,[7] but other sulfonamide compounds (sulfapyridine, sulfathiazole and sulfadiazine) were recovered from the aqueous only in small quantities. Powdered sulfanilamide applied to the conjunctival sac of the rabbit resulted in a considerably higher concentration in the aqueous than that produced by the salve. However, there was slight damage to the corneal epithelium, which may have increased its permeability to the powdered form of the drug.

According to Vail,[8] "the local use of sulfanilamide ointment or powder, in external ocular lesions particularly, is worthy of further trials and studies and is of much promise." Ointments containing sulfonamide compounds in approximately 5 per cent concentration have been employed in the treatment of ocular infections.[9] Because of the apparent growing importance of these substances in the treatment of civilian and military war wounds, it seemed desirable to study the effect of local treatment with an ointment containing 5 per cent of sulfonamide compounds on the healing of experimental wounds of the cornea of rabbits. The wounds were produced (*a*) with sterile instruments (Graefe's knives, wide keratomes, Hippel's trephines) and (*b*) with similar instruments previously infected with hemolytic staphylococci.

MATERIALS AND METHODS

Animals.—Male albino rabbits, weighing 2,000 to 2,500 Gm., were used. The animals were anesthetized by an intravenous injection of pentobarbital sodium, supplemented with topical instillation of 1 per cent butacaine sulfate into the conjunctival sac.

Experimental Wounds.—The following types of wounds were produced in the cornea:

A. Incised wounds causing no substantial loss of the corneal tissue.

1. Superficial lesions, measuring approximately 4 mm. in length and 0.4 mm. in depth, involving the outer layers of the cornea but not penetrating Descemet's membrane.

2. Deep lesions, measuring approximately 5 mm. in length, perforating Descemet's membrane and penetrating the anterior chamber.

B. Incised wounds causing substantial loss of the corneal tissue. These wounds were produced with a guarded trephine and are designated as "trephine wounds."

1. Superficial trephine wounds, with removal of a cylindric portion of the corneal tissue measuring approximately 3 mm. in diameter and 0.4 mm. in depth. This section of the cornea did not involve Descemet's membrane.

2. Deep trephine wounds, producing a punched-out lesion measuring approximately 1.5 mm. in diameter, perforating Descemet's membrane and penetrating the anterior chamber.

Infection.—A twenty-four hour broth culture of Staphylococcus aureus haemolyticus was freshly diluted with sterile broth (1 : 10). The instruments were immersed for two minutes into the diluted culture and then used immediately to produce the different types of wounds of the cornea. This micro-organism was selected because of its frequent occurrence in infected ocular wounds.

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7. Chinn, H., and Bellows, J. G.: Corneal Penetration of Sulfanilamide and Some of Its Derivatives, Arch. Ophth. **27**:34-39 (Jan.) 1942.

8. Vail, D. J.: Sulfanilamide Compounds in Ophthalmology, editorial, Am. J. Ophth. **24**:339-341 (March) 1941.

9. Guyton, J. S.: Local Use of Sulfanilamide Compounds in the Eye, Am. J. Ophth. **24**:292-297 (March) 1941.

Treatment.—A 5 per cent sulfanilamide ointment and a 5 per cent sulfadiazine ointment were prepared according to Guyton's formula.[9a] Equal parts of the two preparations were mixed and used in amounts of approximately 0.1 Gm.

Of the two compounds, sulfanilamide is "the drug of choice" for topical use in wounds because of its known antibacterial activity and its high solubility and diffusibility and because it appears to be the least harmful to regenerating tissues of the commonly used sulfonamide compounds. The addition of sulfadiazine, which is equally antibacterial but which is absorbed and excreted more slowly than sulfanilamide, was made to obtain a prolonged chemotherapeutic effect.

Time of Treatment.—The first local treatment was given shortly after the production of the wound, usually at 9 a. m.; a second application of ointment was made at 1 p. m. and a third at 5 p. m. Thereafter, local treatment was continued every day at 9 a. m., 1 p. m. and 5 p. m. until the eye showed clinical signs of healing. If the condition of the eye did not improve within two weeks, treatment was discontinued.

Clinical Examination of the Eyes.—The eyes were examined each morning before application of the treatment. The cornea was examined with a magnifying device and with focal and diffuse illumination. The specular reflex was often observed. In addition, the eyes were stained with a 2 per cent solution of fluorescein sodium. The wound was considered clinically healed when the cornea did not stain with the dye and the other gross signs and symptoms of conjunctivitis, iritis and keratitis had subsided.

Laboratory Examinations.—Material obtained with a sterile cotton swab from the corneal surface was examined before traumatization and repeatedly during the course of the treatment. Cultures were made on solid and in liquid mediums. Histologic studies were made on 39 eyes after the death of the animals. The eyes were fixed in Helly's fluid, and sections were stained with hematoxylin and eosin.

RESULTS

Experimental wounds were produced on 88 corneas. Three animals were killed within fifteen minutes after traumatization and the eyes preserved to illustrate the various types of lesions produced. Of the remaining 82 eyes, 32 were treated with the sulfonamide ointment, 17 received the ointment base without the sulfonamide compound and 33 were not treated.

Healing of Superficial and Deep Incised Wounds of the Cornea.—A superficial incision of the cornea was produced with a sterile instrument on both eyes of 6 rabbits. Of the 12 eyes, 4 were treated with the sulfonamide ointment, 4 received the ointment base without the sulfonamide compound and 4 were not treated.

In a second group of 6 rabbits an incision penetrating into the anterior chamber of both eyes was produced with a sterile keratome. As in the first group, 4 eyes were treated with the sulfonamide ointment and 4 eyes with the ointment base alone, and 4 eyes received no treatment.

The results obtained on these 24 eyes are summarized in table 1.

There was no significant difference in the average healing time of superficial corneal lesions between the wounds treated with the sulfonamide ointment, the wounds treated with the ointment base alone and the wounds receiving no treatment. The average healing time of deep corneal incisions treated with sulfonamide ointment was considerably longer than that of the untreated control wounds. A similar delay in the healing process was also observed when the ointment base alone was used. Therefore, the retardation in the healing processes in this group cannot be attributed to the action of the sulfonamide compounds.

9a. Guyton.[9] The formula employed was as follows: Ten parts of the sulfonamide compound (sulfanilamide or sulfadiazine) was dissolved in 25 parts of boiling water, and 4 parts of sodium alginate, in 75 parts of boiling water. These solutions were mixed and stirred until cool. Sixteen parts of anhydrous wool fat, 1 part of sodium chloride dissolved in 4 parts of water and 78 parts of white petrolatum base were added to the sulfonamide–sodium alginate mixture and stirred until a smooth ointment was obtained.

A slight conjunctival reaction, lasting for approximately six hours after the traumatization, was the only clinical manifestation observed in some of the eyes with superficial incised wounds. When deep incisions penetrating into the anterior chamber were produced, a pronounced conjunctival reaction, with some discharge, and slight or moderate iritis were frequently noted. These reactions subsided within one to three days after the experimental incision. The anterior chamber was reformed in from six to twenty-four hours after the incision.

In a third group of 6 rabbits superficial and deep incised wounds of both corneas were produced with instruments infected with hemolytic staphylococci. Six eyes were treated with the sulfonamide ointment, and 6 eyes were not treated. The ointment base alone was not employed because it did not accelerate healing of noninfected wounds and therefore could not be expected to be effective in the presence of micro-organisms.

In this group, again, the tendency of the superficial wounds to heal was good. The average healing time of the eyes treated with sulfonamide ointment was 40 hours, and that of the untreated controls was 24 hours. A slight conjunctival reaction of short duration was the only clinical symptom in this group.

TABLE 1.—*Effect of Local Treatment with Sulfonamide Ointment* on Healing Time of Superficial and Deep Noninfected Incised Wounds of the Cornea of Rabbits*

Type of Incised Wound	No. of Eyes	Treatment	Time of Healing, Hr.	Average Healing Time, Hr.
Superficial	4	Sulfonamide ointment	22; 22; 24; 46	28.5
	4	Ointment base	22; 24; 30; 48	31
	4	None	24; 24; 24; 24	24
Deep	4	Sulfonamide ointment	24; 96; 96; 120	84
	4	Ointment base	24; 96; 96; 120	84
	4	None	24; 48; 48; 48	42

* Ointment containing sulfanilamide and sulfadiazine in 2.5 per cent concentration each.

Healing of deep incised infected wounds occurred in only 1 eye treated with the sulfonamide ointment for ten days. The other 5 eyes (2 treated and 3 untreated) became progressively worse. Within twenty-four hours after traumatization, inflammatory reactions of the cornea, conjunctiva and iris appeared. There was also considerable mucopurulent discharge. Keratitis, conjunctivitis and iritis became more evident during the next three to four days, and a hypopyon ulcer frequently developed. At this time the eyes presented marked to extensive conjunctivitis and keratitis, with pannus formation and ulceration of the cornea and moderate to severe iritis and uveitis. The end result was complete blindness from endophthalmitis or phthisis bulbi. The staining reactions remained positive throughout the course of the experiments.

Our observations on the effect of local treatment with a 5 per cent sulfonamide ointment on the healing time of incised experimental wounds of the cornea of rabbits gave the following results:

Superficial wounds, both noninfected and infected, healed in from 22 to 48 hours. The average healing time of the treated eyes and that of the untreated control eyes did not show significant differences.

Deep noninfected wounds healed in from 24 to 120 hours. The average healing time of the untreated control eyes was 42 hours, and that of the treated eyes was 84 hours. The sulfonamide ointment and the ointment base alone showed the same retarding effect on the average healing time; therefore, the retardation cannot be attributed to the action of the sulfonamide compounds. Healing of deep

infected wounds occurred in only 1 eye, which was treated with sulfonamide ointment for ten days. In the other 5 eyes (2 treated and 3 untreated) blindness developed from endophthalmitis or phthisis bulbi.

Healing of Superficial and Deep Trephine Wounds of the Cornea.—A superficial trephine wound was produced with a sterile instrument on the cornea of both eyes of 7 rabbits. Of the 14 eyes, 5 were treated with the sulfonamide ointment, 5 received the ointment base alone and 4 were not treated.

In another group of 9 rabbits, a trephine wound perforating Descemet's membrane was produced with a sterile instrument in both eyes. Six eyes were treated with the sulfonamide ointment; 4 eyes received the ointment base alone and 8 eyes had no treatment.

The results obtained with these 32 eyes are given in table 2.

There was no significant difference in the average healing time of superficial trephine wounds of the cornea between the eyes treated with sulfonamide ointment and the untreated control eyes. The average healing time of the eyes treated with the ointment base alone was notably prolonged in 2 instances. Similarly, the differences in the average healing time of deep trephine wounds perforating Descemet's

TABLE 2.—*Effect of Local Treatment with Sulfonamide Ointment* on Healing Time of Superficial and Deep Noninfected Trephine Wounds of the Cornea of Rabbits*

Type of Trephine Wound	No. of Eyes	Treatment	Time of Healing, Hr.	Average Healing Time, Hr.
Superficial	5	Sulfonamide ointment	96; 96; 96; 120; 144	110.4
	5	Ointment base	96; 120; 192; 240; 264	182.4
	4	None	48; 120; 120; 192	120
Perforating	6	Sulfonamide ointment	48; 96; 144; 144; 168; 168	128
	4	Ointment base	120; 144; 144; 168	119
	8	None	96; 96; 96; 96; 120; 120; 120; 168	114

* Ointment containing sulfanilamide and sulfadiazine in 2.5 per cent concentration each.

membrane were slight. In the rabbits receiving the deep trephine wound, the untreated control eyes showed the shortest average healing time.

The clinical picture in the rabbits that had received trephine wounds of the cornea consisted in moderate to pronounced conjunctival reaction, with considerable mucopurulent discharge and varying degrees of keratitis and anterior uveitis. These symptoms usually appeared within a few hours after the injury, became more pronounced after twenty-four hours and gradually subsided.

Finally, superficial and deep trephine wounds were produced in the corneas of 7 rabbits with a trephine infected with hemolytic staphylococci. Seven eyes were treated with the sulfonamide ointment, and 7 eyes were not treated. The ointment base alone was not employed because no beneficial action on healing of the wounds could be expected from this ointment in the presence of micro-organisms.

In these animals, healing occurred after treatment with the sulfonamide ointment in 5 eyes (in 3, 3, 7, 9 and 14 days respectively) and without treatment in 3 eyes (in 3, 4 and 8 days respectively), while no improvement was seen in the remaining 6 eyes (2 with and 4 without treatment with the sulfonamide ointment). The clinical picture in this group showed more severe involvement of the conjunctiva, cornea and iris.

Local treatment with sulfonamide ointment of trephine wounds of the cornea of rabbits gave the following results:

The average healing time of superficial noninfected wounds of both treated eyes and untreated control eyes did not show significant differences; application of the ointment base alone retarded the healing considerably in 2 eyes.

Deep noninfected wounds healed equally well whether the eyes were treated or were not treated.

Healing of wounds produced with infected trephines occurred in 5 eyes after treatment with the sulfonamide ointment for periods varying from three to fourteen days and in 3 untreated control eyes. No healing was observed in 2 treated and in 4 untreated eyes.

BACTERIOLOGIC STUDIES

A total of 143 cultures of material obtained from 48 eyes was examined. The material from the corneal surface before traumatization contained a variety of gram-positive and gram-negative micro-organisms, the most frequent being anhemolytic staphylococci, other gram-positive cocci and Bacillus subtilis. Essentially the same microbic flora was obtained in cultures of material obtained at daily intervals up to seven days after traumatization from both the treated and the untreated eyes. However, a notable inhibition of bacterial growth was observed in cultures of material from 8 of 24 eyes that had received treatment with sulfonamide ointment for one or two days. No inhibition of bacterial growth occurred in cultures of material from untreated eyes or from eyes receiving the ointment base alone.

Material from the corneal surface obtained a few minutes after traumatization of the eyes with instruments infected with Staph. aureus haemolyticus yielded these organisms in pure culture. However, cultures of material taken after twenty-four and forty-eight hours from both the treated and the untreated eyes again contained the mixed bacterial flora previously described.

There was no evident relation between the healing time of the experimental wounds and the results of bacteriologic studies.

HISTOLOGIC STUDIES

Histologic studies were made on 39 eyes. Three rabbits were killed within fifteen minutes after traumatization in order to study the extent of the experimental wounds.

Photomicrographs of the two types of incised and trephine wounds, both superficial and deep, are shown in figures 1 to 4. It will be seen (figs. 1 and 2) that the superficial wounds pierced the epithelium and Bowman's membrane and penetrated the corneal stroma but did not involve Descemet's membrane. The deep wounds (figs. 3 and 4) involved all the layers of the cornea and penetrated the anterior chamber.

The histologic appearance of eyes which were considered "clinically healed" after receiving different types of experimental wounds of the cornea is illustrated in figures 5 to 12. The continuity of the epithelial layer covering the corneal surface was completely restored in every instance; this accounts for the lack of staining with the fluorescein solution.

Photomicrographs of 4 eyes which had received superficial incised or trephine wounds are shown in figures 5 to 8. These pictures were obtained at the time of "clinical healing," which occurred in from 24 to 192 hours. There was marked proliferation of the epithelium at the site of the previous injury. A slight degree of acute inflammation was seen in wounds produced with infected instruments (fig. 6). In trephine wounds, which usually required a longer time for healing, the corneal stroma at the site of the previous injury appeared as a healed scar, containing fibroblasts and a few large macrophages (figs. 7 and 8).

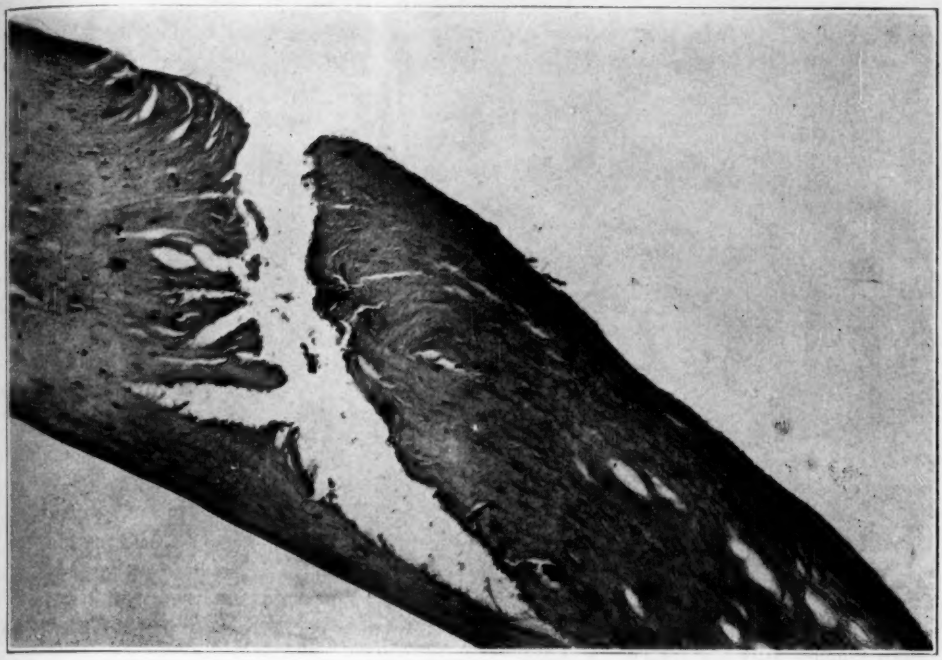

Fig. 1.—Extent of superficial incised wound in the rabbit's cornea. The animal was killed within fifteen minutes after the injury. × 120.

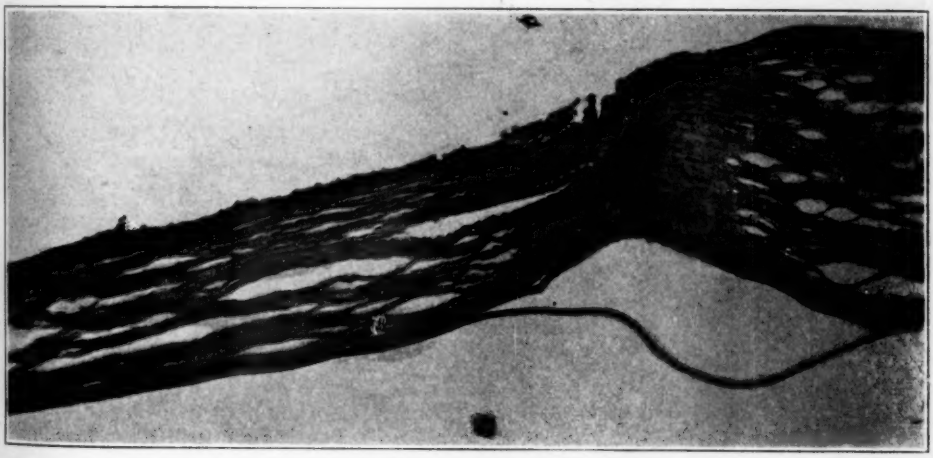

Fig. 2.—Extent of superficial trephine wound in the rabbit's cornea. The animal was killed fifteen minutes after the injury. × 120.

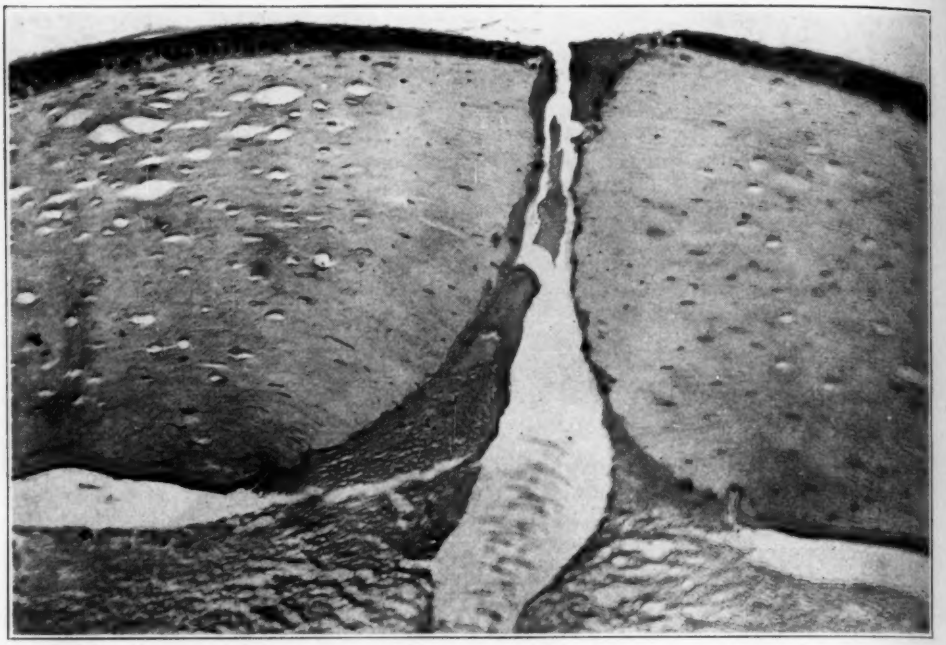

Fig. 3.—Extent of deep incised wound in the rabbit's cornea. The animal was killed fifteen minutes after the injury. × 120.

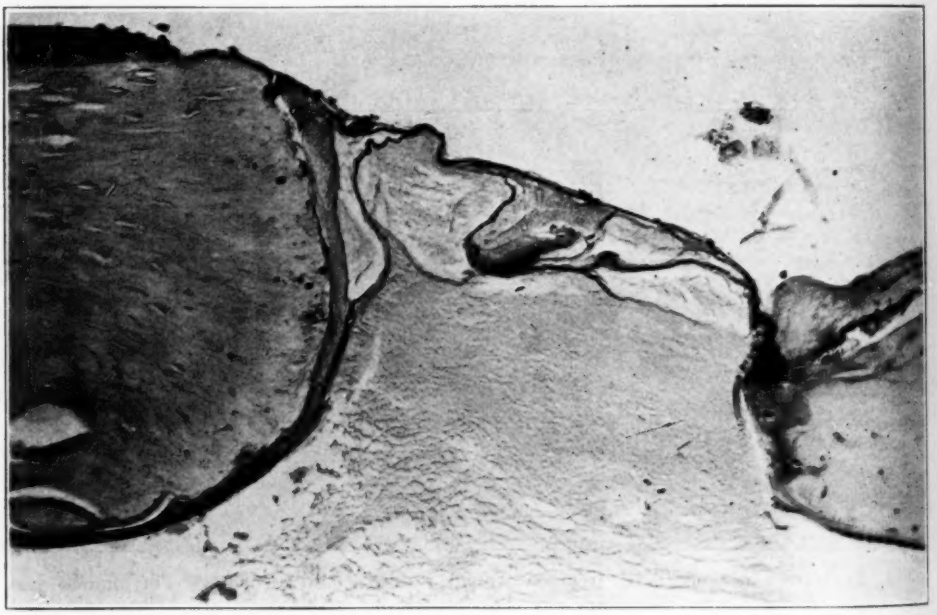

Fig. 4.—Extent of deep trephine wound in the rabbit's cornea. The animal was killed fifteen minutes after the injury. × 120.

The healing process of deep incised wounds showed thickening of the surface epithelium at the site of the injury, with ingrowth of the epithelium into the wound. The sections shown in figures 9 and 10 were obtained from the same eye at different levels; the corneal stroma still presents a gap in one section (fig. 10), although the epithelium and endothelium apparently had already completely regenerated.

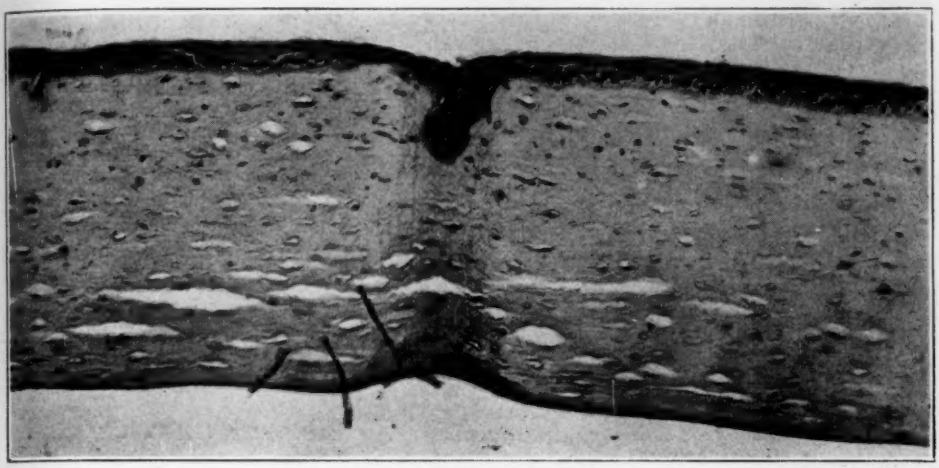

Fig. 5.—Healing of superficial incised wound in the rabbit's cornea produced with a sterile instrument, showing proliferation of regenerated epithelium. The eye was treated with an ointment containing sulfonamide compounds in 5 per cent concentration. The lesion healed in 24 hours, and the animal was killed eighteen hours later. × 120.

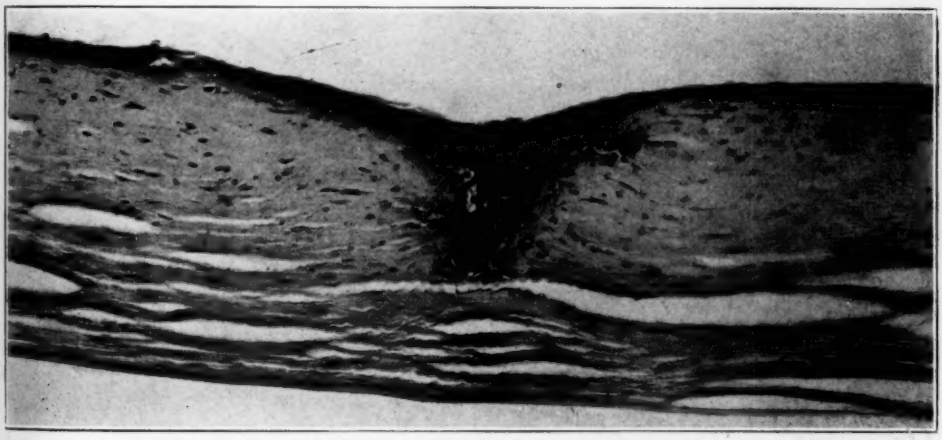

Fig. 6.—Healing of superficial incised wound in the rabbit's cornea produced with an infected instrument, showing thickening of regenerated epithelium and a slight degree of reactive inflammation. The lesion was treated with the sulfonamide ointment and healed in 24 hours. The animal was killed twenty-four hours later. × 120.

A typical scar with numerous fibroblasts was seen in eyes in which the healing time had been prolonged to 10 days after injury with an infected keratome (fig. 11). The healing process of a deep trephine wound of a rabbit's cornea is shown in figure 12.

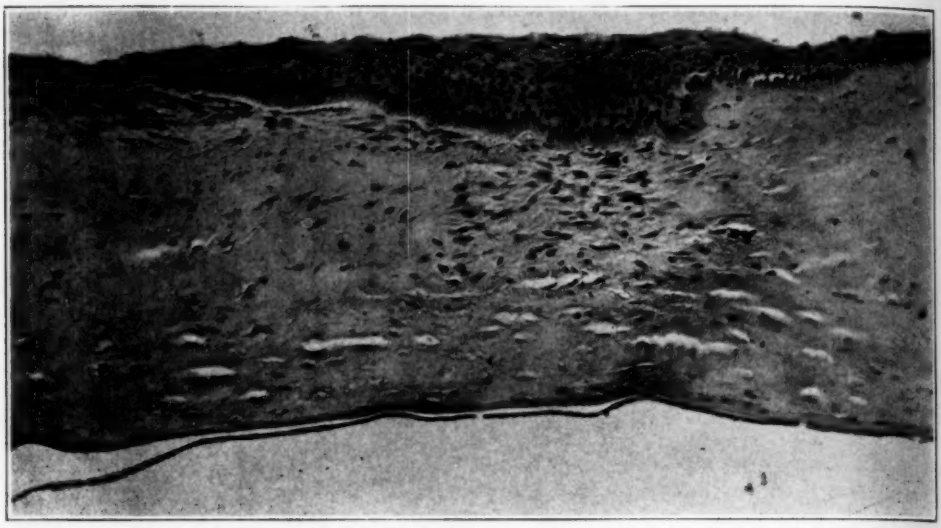

Fig. 7.—Healing of superficial trephine wound in the rabbit's cornea produced with a sterile instrument. No treatment was administered. The wound healed in 8 days. × 120.

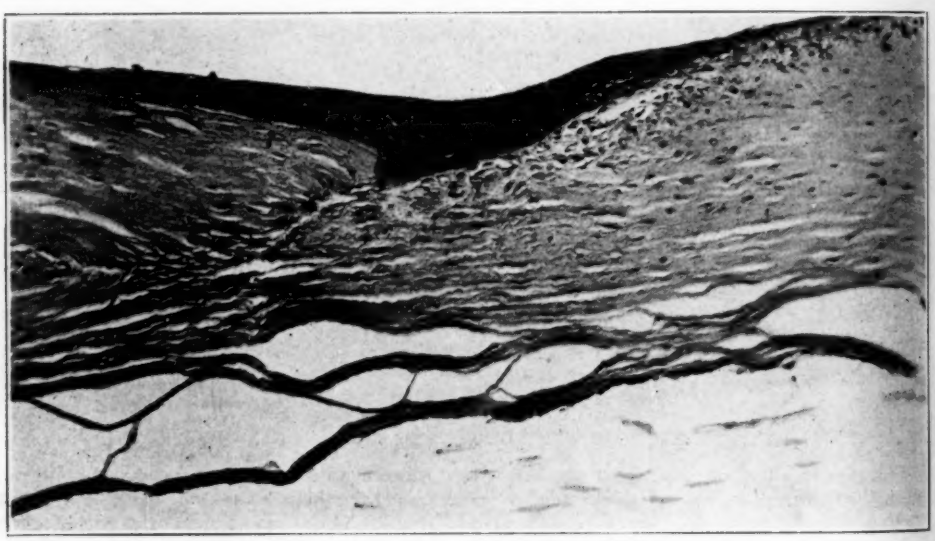

Fig. 8.—Scar following superficial trephine wound in the rabbit's cornea produced with an infected trephine. The lesion, treated with the sulfonamide ointment, healed in 3 days. The animal was killed twenty-four hours later. × 120.

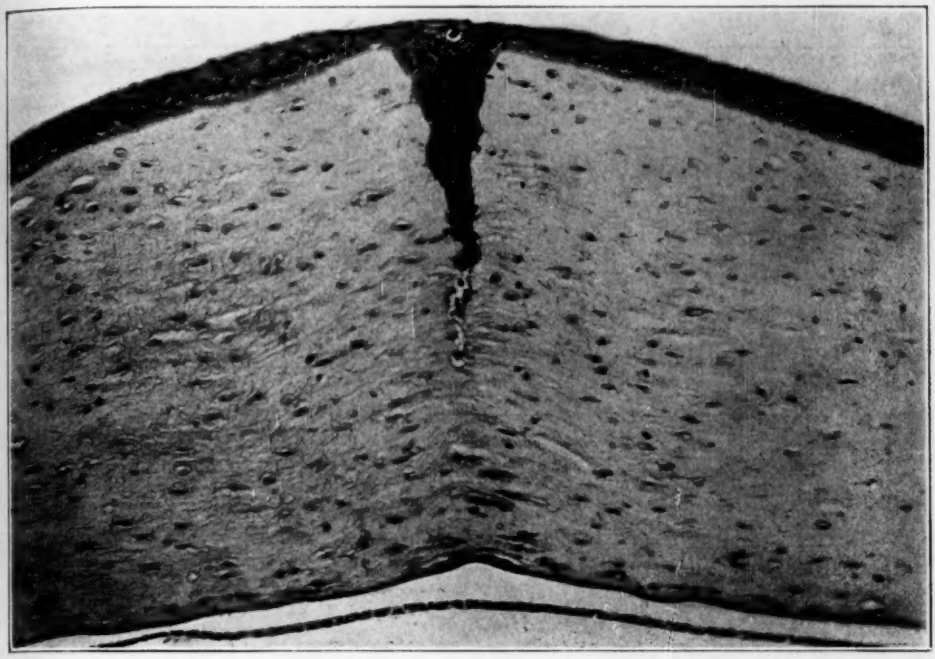

Fig. 9.—Healing of a perforating incision through Descemet's membrane of the rabbit's cornea produced with a sterile keratome, showing ingrowth of epithelium into the wound. No treatment was given. The wound healed in 24 hours, and the animal was killed eighteen hours later. × 120.

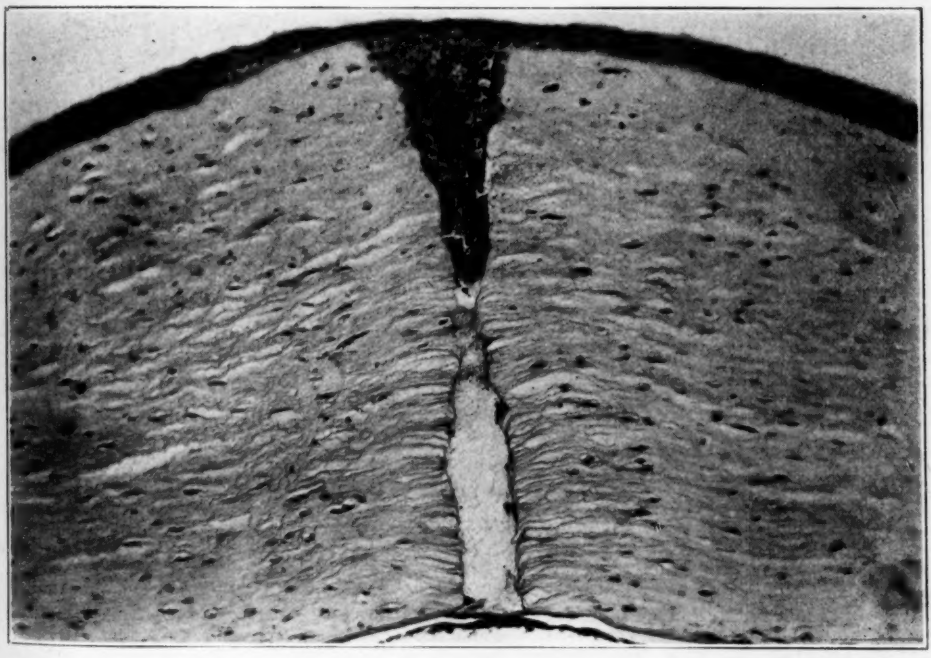

Fig. 10.—Another area of the cornea from the same eye from which the section shown in figure 9 was taken. Epithelial and endothelial regeneration is completed, but there is still a gap in the corneal stroma. × 120.

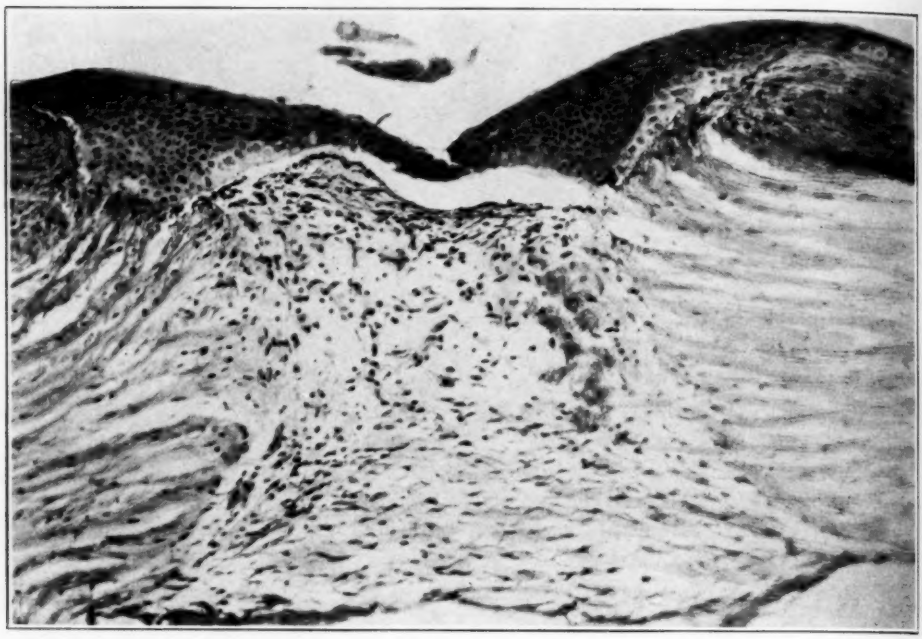

Fig. 11.—Scar following a deep incision produced in the rabbit's cornea with an infected instrument. The wound, treated with the sulfonamide ointment, healed in 10 days. × 120.

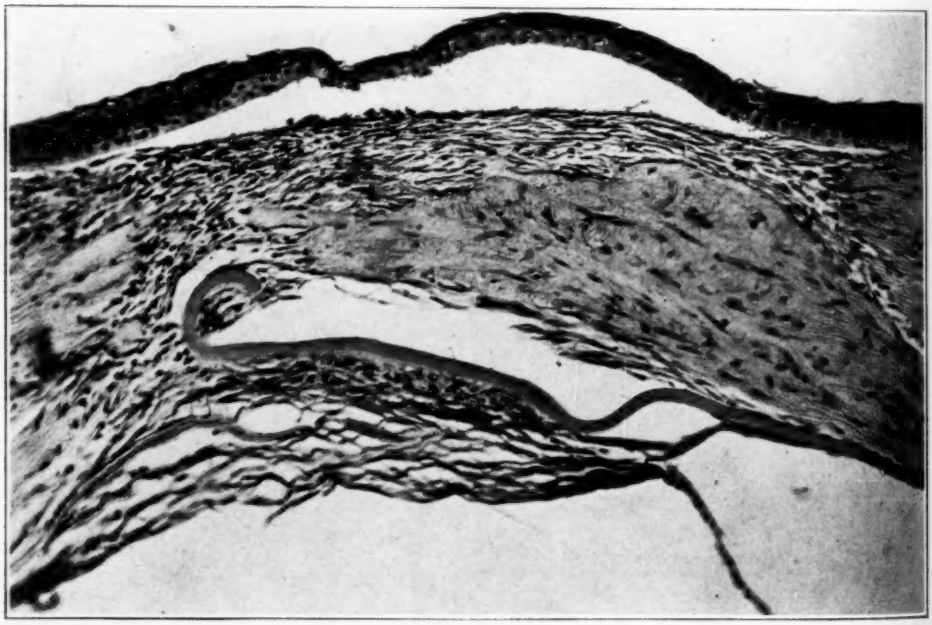

Fig. 12.—Healing of a deep trephine wound in the rabbit's cornea produced with an infected instrument. The lesion, treated with the sulfonamide ointment, healed in 7 days. × 120.

COMMENT

Healing of wounds in the presence of sulfonamide compounds is still a controversial question. Some investigators [10] have reported retardation of the healing, and other workers [11] have observed no evidence of the interference of sulfanilamide with the process of normal healing. The local toxic effects of sulfonamide compounds on the ocular tissues have been recently investigated by Bellows and Gluckman.[12] According to these authors, sulfonamide compounds cause severe damage to the cornea of rabbits in the absence of normal epithelium. The average healing time of the eyes treated with the sulfonamides was 5.1 days and that of the untreated control eyes was 13.3 days.

In our experience, the average healing time of corneal wounds produced with sterile instruments was usually somewhat prolonged in eyes treated locally with the sulfonamide ointment. This was especially noticeable in the eyes that received a deep incised wound (table 1). However, local treatment with the ointment base alone also retarded healing of the wound; frequently this retardation was greater than that observed in the eyes treated with the sulfonamide ointment. Therefore, our results do not permit the conclusion that the sulfonamide compounds were responsible for the delay in healing of the wound, but they indicate that the introduction of foreign material into a sterile wound may interfere with its healing.

In eyes that received experimental wounds with infected instruments the average healing time could not be determined because 11 of the 26 eyes did not heal but became progressively worse. Good results were observed with the sulfonamide ointment. In the eyes that had received trephine wounds with infected instruments, healing occurred in 5 of 7 eyes treated with the sulfonamide ointment and in only 3 of the 7 untreated control eyes. These figures are too small to be of statistical significance, but they apparently demonstrate the effectiveness of the sulfonamide ointment in treatment of infected corneal wounds.

Objection might be raised to our criteria for the determination of "clinical healing," namely, the absence of staining with fluorescein and the regression of the inflammatory symptoms. However, at the stage of clinical healing the continuity of both the surface epithelium and the endothelial lining is completely restored, while the regeneration of the corneal stroma may still be incomplete (fig. 10). Since an intact epithelial surface offers protection against infection by invading micro-organisms, no further local treatment with sulfonamide compounds would be required. Therefore, the criteria employed were sufficient to determine the length of time that therapy with the sulfonamide compounds should be continued.

Local application of a 5 per cent sulfonamide ointment, containing equal amounts of sulfanilamide and sulfadiazine, usually did not accelerate the healing time of

10. Veal, J. R.; Klepser, R. G., and De Vito, M. P.: Preparation of Superficial Wounds for Skin Grafting by Local Use of Sulfanilamide and Sulfanilamide-Allantoin Ointment, Am. J. Surg. **54**:716-720 (Dec.) 1941. Bick, E. M.: Observation on the Topical Use of Sulfonamide Derivatives, J. A. M. A. **118**:511-513 (Feb. 14) 1942. Taylor, F. W.: The Misuse of Sulfonamide Compounds, ibid. **118**:959-961 (March 21) 1942.

11. Key, J. A., and Burford, T. H.: The Local Implantation of Sulfanilamide in Compound Fractures, South. M. J. **33**:449-455 (May) 1940. Harbison, S. P., and Key, J. A.: Local Implantation of Sulfanilamide and Its Derivatives in Wounds: Its Relation to Wound Healing and to Peritoneal Adhesions, Arch. Surg. **44**:22-26 (Jan.) 1942. Klepser, R. G.: Problems in the Local Use of Sulfonamides, M. Ann. District of Columbia **11**:211-213 (June) 1942.

12. Bellows, J. G., and Gluckman, R., cited by Bellows.[1c]

experimental wounds produced with sterile instruments on the cornea of rabbits; its use, therefore, is of little therapeutic significance. This, of course, does not preclude the possibility that higher concentrations of sulfonamide compounds, a modification in the composition of the ointment or the local use of powdered sulfonamide compounds might not have a different effect and prove to be more useful than the sulfonamide ointment used in this series. Experimental work along these lines is in progress.

In agreement with Bellows,[1c] our results indicate that the local use of the sulfonamide compounds can be limited at this time to cases in which chances of infection prevail. The results obtained with the sulfonamide ointment in our series of eyes with wounds produced with infected instruments are highly promising.

SUMMARY AND CONCLUSIONS

1. Superficial and deep wounds, with or without substantial loss of corneal tissue, produced with sterile instruments in the eyes of rabbits were treated locally with an ointment containing sulfonamide compounds in 5 per cent concentration (2.5 per cent sulfanilamide and 2.5 per cent sulfadiazine) and with the ointment base alone. The average healing times of the wounds of the cornea treated with the sulfonamide ointment and with the ointment base alone were usually greater than the average healing time of the untreated control eyes.

2. Healing of deep incised wounds produced with a keratome infected with Staph. aureus haemolyticus occurred in 1 of 3 rabbit eyes treated with the sulfonamide ointment, but not in 3 untreated control eyes. Healing of trephine wounds produced with instruments infected with Staph. aureus haemolyticus occurred in 5 of 7 eyes treated with sulfonamide ointment, but only in 3 of 7 control eyes.

3. Bacteriologic cultures of material obtained from the corneal surface of the eyes showed a mixture of gram-positive and gram-negative micro-organisms, staphylococci and B. subtilis being the most frequently observed. A notable inhibition of the bacterial growth was observed in cultures of material from 8 of 24 eyes that had received treatment with the sulfonamide ointment but not in cultures of material from the control eyes. Essentially the same microbic flora was noted in cultures of material obtained at daily intervals during the process of healing. There was no demonstrable relation between the healing time of experimental corneal wounds and the bacterial flora.

4. Histologic sections of corneas of rabbits considered to be "clinically healed" revealed that the continuity of the surface epithelium was restored. There was pronounced thickening of the epithelium at the site of the previous injury. In wounds that required several days for healing, typical scar tissue was observed at the site of the previous wound. This was particularly noticeable in the wounds with infected instruments. Regeneration of the surface epithelium was observed at a time when the corneal stroma still presented lack of continuity.

5. Local use of an ointment containing sulfonamide compounds in 5 per cent concentration did not accelerate the healing of superficial or deep incised or trephine wounds of the cornea of rabbits if sterile instruments were used to produce the injury. The ointment was of value in the treatment of wounds produced with instruments that were infected with Staph. aureus haemolyticus.

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INFLUENCE OF PROLONGED WEARING OF MERIDIONAL SIZE LENSES ON SPATIAL LOCALIZATION

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When a meridional size lens [1] is placed with its axis in the vertical position (at 90 degrees) in front of one eye of a normal observer, the retinal image of that eye is enlarged in the horizontal meridian. Since horizontal disparity of the retinal images is responsible for stereoscopic effects, the observer will experience typical changes in the appearance of his environment. If the size lens is placed in front of the right eye, objects located in the right half of the observer's field of vision appear larger yet farther away from him than objects of the same size situated at the same distances from the observer but located in the left half of his field of vision. A flat desk top will appear to be slanting down on the right side and slanting up on the left side; a wall perpendicular to the observer's line of gaze will appear farther away from him on the right side and closer to him on the left side; the ground on which the observer walks is tipped downward on the right and upward on the left side, as though he were walking on the side of a hill. If he holds his hands in front of his eyes, the right hand will seem to be larger. At the same time the shape of the objects will appear distorted. The top of the desk and the wall assume the form of a trapezoid; a square magazine lying on the right half of the desk, the form of a rectangle, and a round object, such as an ash tray or a round wash basin, the form of an ellipse. If the observer looks into a mirror he will find that his face has become asymmetric, with the right side protruding.[2]

All spatial distortions produced by a size lens placed at axis 90 in front of one eye can be explained in a relatively simple manner, on a geometric basis. Assume that an observer's visual lines converge on a point F (fig. 1) on a plane on which there are two points, P and N, seen in peripheral vision. Introduce now in front of the right eye a size lens which magnifies the horizontal meridian only. All distances are magnified for the right eye, and the distance PFN is increased to $_{\pi}Fv$. The object point P, originally imaged on the retinal point p_r in the right eye, now stimulates the more temporal point p'_r; the image of the object point N is displaced in the right eye from n_r to n'_r. No change in the image of the left eye has occurred. The horizontal disparity which is thus created results in a stereoscopic effect. Object point P appears to have advanced and object point N to have receded, since only points situated objectively at P' and N' could fulfil the condition of stimulating simultaneously the retinal elements p_l, p'_r and n_l n'_r. As a result, the plane PFN appears rotated around the fixation point F. The

From the Dartmouth Eye Institute, Dartmouth Medical School.

1. These lenses have no appreciable refractive power but magnify the retinal image. They are ground as over-all size lenses, having the same magnification in all meridians, or as meridional size lenses, having a specified magnification in one meridian but no magnifying effect in the meridian at right angles. The designation of the axes and effective meridians of the size lenses is analogous to that of cylindric refractive lenses.

2. The importance of the relative size and shape of the ocular images in binocular spatial localization was recognized in the early stages of the research in aniseikonia. A full description of the result of new investigations will be given by A. Ames Jr. in publications now in preparation.

amount of rotation, as expressed by the angle Ψ, is proportional to the magnification introduced by the lens and is given by the formula $\tan \Psi = \left[\frac{M-1}{M+1} \right] \frac{b}{a}$, in which M is the magnification, b the fixation distance and a one-half the interpupillary distance.[3]

The spatial distortions, although in the same direction for all normal observers, are not experienced in all environments and by all observers with the same intensity. Spatial orientation in man, particularly depth perception, is based on two groups of factors. One group can be derived only from the simultaneous stimulation of the two retinas; it comprises the psychophysiologic results produced by the stimulation of disparate retinal elements. They are designated as binocular or disparity factors. The other group can be obtained from the stimulation of one eye alone. It comprises such factors as perspective, size and form of known objects; the knowledge of what is level and what perpendicular, etc. These factors are the uniocular

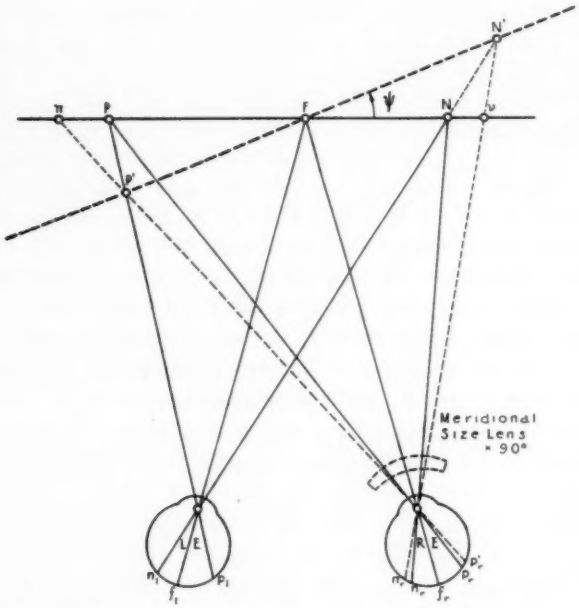

Fig. 1.—Apparent rotation of a vertical plane due to the magnification of the image of one eye in the horizontal meridian.

clues, not based on retinal disparities. The disparity factors form the foundation of binocular vision and true stereopsis. They result in the most exact *perception* of the relation of objects in space; the uniocular clues allow an *interpretation* of the spatial relation of objects, but this interpretation is never as accurate as the actual perception afforded by the disparity factors.

It is important for the purpose of scientific analysis to emphasize the difference between these two sets of factors. But unerring orientation in space is made possible only by the constant interaction of both sets. The disparity factors are as such unchangeable; i. e., the simultaneous stimulation of the same two disparate retinal elements lying within fusional areas causes—in the absence of strong

3. Ogle, K. N.: Analytical Treatment of the Longitudinal Horopter: Its Measurement and Application to Related Phenomena, Especially to the Relative Size and Shape of Ocular Images, J. Optic. Soc. America **22**:665, 1932; Die mathematische Analyse des Längshoropters, Arch. f. d. ges. Physiol. **239**:748, 1938.

uniocular factors—the stimulating object point always to be localized in the same position in the subjective space of the observer. But the actual experience of the relation of objects in space is constantly modified and rectified by the uniocular clues. If a condition exists in which the information conveyed by the disparity clues is in conflict with the information conveyed by the uniocular clues, the latter may dominate if the field of vision contains a sufficient amount of perspective elements, such as are present in ordinary surroundings indoors. Also, the response to stereoscopic stimuli varies not only with different persons but with the same observer at different times. It depends on a number of circumstances whether the disparity factors or the uniocular clues will prevail.

Every person with normal binocular vision experiences the distortional effect of meridional size lenses to the theoretically expected degree if his field of view contains a minimum of perspective elements. Such a field of view exists in natural surroundings, in the underbrush of a forest or on a lawn. It can be created artificially in laboratory experiments by using instruments in which the field of view is as devoid as possible of perspective and form factors. Such an instrument is, for instance, the apparatus by means of which the empiric horopter [4] is determined. The curve of the longitudinal empiric horopter always undergoes a rotation about a vertical axis through the fixation point when a difference in the size of the ocular images is introduced in the horizontal meridian (fig. 2).[5] This rotation is strictly proportional to the amount of magnification introduced and has been termed by Ogle "the geometric effect" of the size lenses on the longitudinal horopter, because the geometric explanation conforms so closely to the subjective spatial localization.[6]

It is known now what takes place when a normal person introduces in front of one eye a meridional size lens at axis 90. The problem which arises and which I have attempted to solve is this: What happens to the appearance of space and to an observer's functioning within space when a meridional size lens is worn constantly for a certain length of time? Do the spatial distortions of the normal surroundings remain unchanged? Does the rotation of the horopter curve remain the same? Does the capacity of compensating for artificially introduced meridional aniseikonic errors exist? And if compensation should occur, is it due to a physiologic change which reduces the artificially created disparity, or is it the result of a modification of the interpretation of the relation of objects in space due to an increasing effect of the uniocular factors?

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4. The horopter is defined as the locus in space of the object points imaged on corresponding retinal elements of the two eyes. If the corresponding retinal elements were distributed equally on the two sides of the fovea of each eye, the intersection of the visual plane with the surface of the horopter (the "longitudinal" horopter) would be the circle determined by the fixation point and the centers of the pupils of the two eyes (Vieth-Müller circle, fig. 2). Actually, such a regular distribution of the retinal elements—or rather of the spatial values of the retinal elements—does not occur, and the empiric longitudinal horopter differs, therefore, from the Vieth-Müller circle. This difference in shape has been termed the Hering-Hillebrand deviation of the curve of the empiric longitudinal horopter. For near vision fixation distance (40 to 75 cm.) the longitudinal horopter curve is concave toward the observer and lies somewhere between the Vieth-Müller circle and the objective frontoparallel plane (fig. 2). Owing to the discrepancies in the distribution of the spatial values of the retinal elements between the two eyes, the curve of the empiric longitudinal horopter is frequently not symmetric.

5. Ames, A., Jr.; Ogle, K. N., and Gliddon, G. H.: Corresponding Retinal Points, the Horopter and Size and Shape of Ocular Images, J. Optic. Soc. America **22**:619, 1932.

6. Ogle, K. N.: Induced Size Effect: A New Phenomenon in Binocular Vision Associated with the Relative Sizes of the Images of the Two Eyes, Arch. Ophth. **20**:604 (Oct.) 1938.

Answers to these questions would be of interest in themselves, since they might permit a direct insight into the interrelation of the disparity and uniocular factors in the total act of space perception. They would also be of practical importance in offering an explanation as to how patients with aniseikonia deal with the problem of spatial orientation. Aniseikonia of clinically significant amount is frequent and always causes a measurable disturbance of spatial orientation.[7] Yet complaints about difficulties arising from such a disturbance are rare, and persons with a clinically significant amount of aniseikonia seem to get around as well as persons with an insignificant amount. How can this apparent contradiction be explained?

Finally, experiments in which size lenses are worn for a period of time may shed some light on the validity of the contention that it is superfluous to correct aniseikonic errors, since many persons become accustomed to even larger differences in the size of the images of the two eyes than are currently equalized in clinical practice by means of iseikonic lenses.

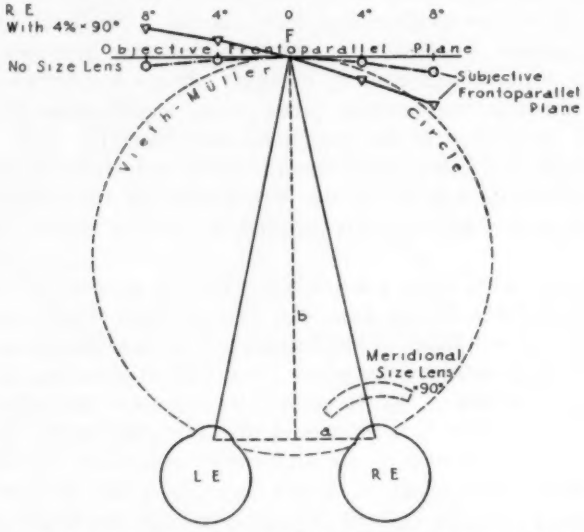


Fig. 2.—Rotation of the curve of the empiric longitudinal horopter (apparent frontoparallel plane) under the influence of a meridional size lens magnifying the horizontal meridian by 4 per cent. (Data of M. E. B.; fixation distance, 40 cm.)

This paper reports results obtained by three observers who wore size lenses at axis 90 in front of one eye for a period of eight to ten days, during which time measurements were made two to three times a day with the horopter apparatus, the space eikonometer, the standard eikonometer and a rotating plane apparatus. These experiments showed that there was a complete adaptation in ordinary surroundings abundant in uniocular factors to the spatial distortions introduced by the size lenses. However, in the instruments with a field of view containing a minimum of perspective factors, the presence of the greater part of the artificially introduced size difference could always be demonstrated.

INSTRUMENTATION AND EXPERIMENTAL PROCEDURE

A. *Instrumentation.*—The instruments used for the determination of the relative difference between the ocular images produced by the wearing of a meridional size lens in front of one eye

7. Ogle, K. N.: Association Between Aniseikonia and Anomalous Binocular Space Perception, Arch. Ophth. **30**:54 (July) 1943.

were the horopter apparatus, the space eikonometer, the standard eikonometer and a rotating plane apparatus with perspective patterns.

The curve of the longitudinal horopter can be determined most rapidly and conveniently by means of the criterion of frontoparallelism. This is achieved by having the observer fixate a vertical wire situated at a given distance in the median plane of his head and having him then set a number of vertical wires to the right and left of the fixation wire as seen in peripheral vision in such a way that all wires appear to him in a plane parallel to his forehead. This subjective or apparent frontoparallel plane is more or less at variance with the

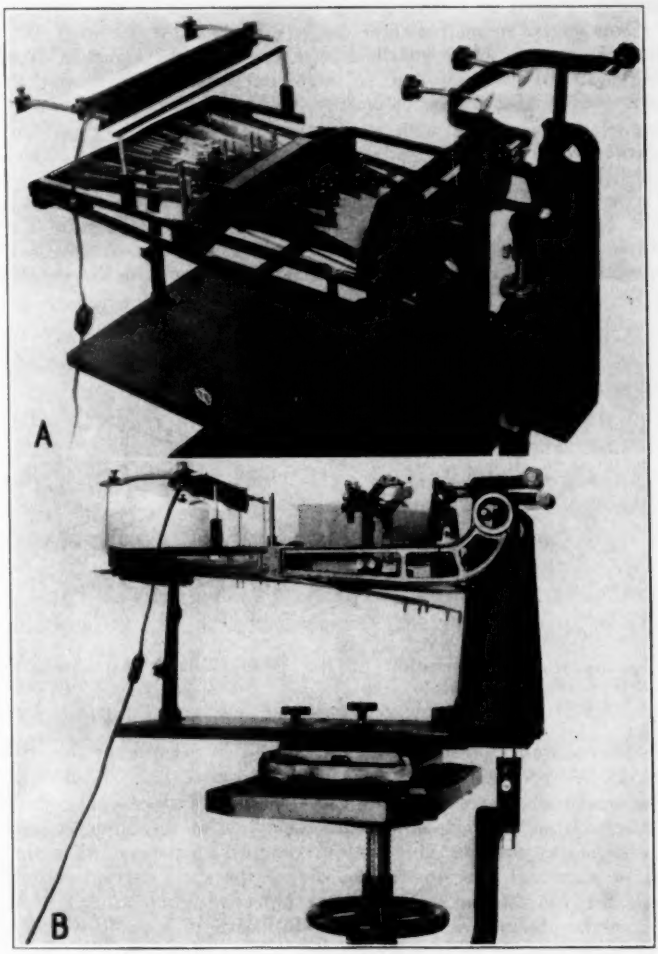


Fig. 3.—The horopter apparatus: *A*, front view; *B*, side view.

objective frontoparallel plane (fig. 2), but the settings for the same observer are constant within very narrow limits of error.

The particular horopter apparatus used in these experiments (fig. 3) was a somewhat simplified instrument of the type described in detail by Ames, Ogle and Gliddon in their fundamental paper.[5] It consists of a number of metal channels, or lanes, which are so arranged as to converge toward a point situated under the midpoint of the basal line of the observer. In these channels metal strips can be moved by means of handles, and on these strips carriers are mounted which support vertical steel wires used as test elements in the determination of the apparent frontoparallel plane. The central wire is mounted at 40 cm. from the midpoint of the observer's basal line and serves as the fixation wire; the other four wires are movable and are located in symmetric lanes at 4 and 8 degrees, respectively,

on each side of the fixation wire. Permanent records of the settings are obtained by means of small punches fastened to the supports of the vertical wires. If the criterion of the common visual directions is to be used for the determination of the horopter curve (nonius horopter) instead of the criterion of frontoparallelism, an attachment is used in front of the wires. This attachment has the form of an illuminated screen with special apertures which cause each of the peripheral wires to be seen in its upper half by one eye and in its lower half by the other eye. The movement back and forth of the wire in the lane causes an apparent sidewise movement in opposite directions of the two monocularly seen halves. The setting is completed when the two halves seem to form a continuous vertical line, since they are then presumably imaged on corresponding vertical sections of the retinas.[8]

The space eikonometer, an instrument recently developed by A. Ames Jr., which was also used in the experiments, has been described by Ogle,[7] and the standard eikonometer and its use have been repeatedly discussed;[9] it is, therefore, sufficient to mention that these instruments were used and to refer to the publications for their description.

The rotating plane instrument with perspective patterns (fig. 4) consisted essentially of white matte cardboard sheets with various patterns (lines, rectangles, circles, ovals, etc.), any one of which could be mounted on a suitable base for rotation about a vertical axis of symmetry. The cardboard could be rotated by means of two metal rods projecting from the sheet carrier toward the observer and extending beyond the aperture through which the observer looked at the patterns. The head of the observer was so adjusted in a head rest that its median plane coincided with a plane through the center of the cardboard and normal

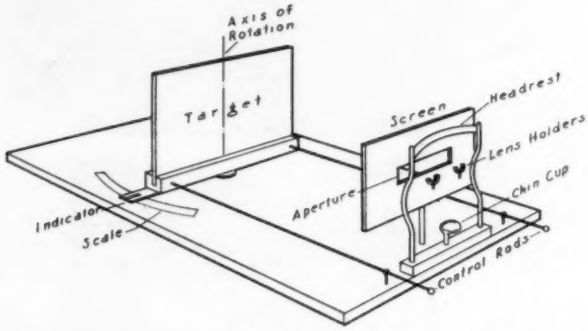


Fig. 4.—Diagrammatic representation of the frontal plane instrument with perspective patterns.

to the objective frontoparallel plane of the instrument. A septum in this median plane prevented the binocular view of extraneous objects. Adjustable cells in front of the observer's eyes allowed the insertion of size lenses or other auxiliary lenses. The center of the cardboard was at 40 cm. from the midpoint of the basal line of the observer, and the cardboard was lighted in such a way that the illumination remained unchanged when the cardboard was rotated. A degree scale and indicator at the end of the sheet carrier permitted an assistant to read the angle between the cardboard and the objective frontoparallel plane of the instrument. The task of the observer was to set the cardboard in a plane which appeared to him to be parallel to his forehead; there were no restrictions as to the fixation of his gaze.

B. *Experimental Procedure.*—The procedure followed in the experiments was simple. For a number of days, usually from four to seven, preliminary measurements were taken the first thing in the morning and late in the afternoon to establish the observer's normal condition. Immediately before and after addition of the size lens, measurements were taken,

8. The data obtained with both types of settings of the horopter apparatus were treated in the way described by Ogle.[3] The actual data (the "spatial curves" of the longitudinal horopter) were transformed into analytic graphs indicating the image size difference present and the slope of the horopter curve.

9. Carleton, E. H., and Madigan, L. F.: Size and Shape of Ocular Images: II. Clinical Significance, Arch. Ophth. **7**:720 (March) 1932. Ogle, K. N., and others: Repeatability of Ophthalmo-Eikonometer Measurements, ibid. **24**:1179 (Dec.) 1940. Burian, H. M.: Clinical Significance of Aniseikonia, ibid. **29**:116 (Jan.) 1942.

and while the size lens was worn the same routine was followed as in the days preceding the experiment proper. One of the observers also regularly took measurements late at night. The size lens was worn for eight to fourteen days, and the observers were never for a single waking moment without it. If the spectacles had to be removed, one eye was always closed until they were again put on; in the morning before the first measurement was taken one eye was as a rule occluded. The observers were requested to keep a diary as to their activities and experiences while wearing the lens. Immediately before and after removal of the lens, measurements were again taken and the routine continued until the observer showed normal readings. This took from four to ten days, so that the three stages of each experiment were completed in from three to four weeks.

The experiments reported were made by three nonpresbyopic observers, all of whom had normal corrected visual acuity and normal binocular vision. One of them is a myope, the other a hyperope and the third an emmetrope. The emmetrope was not accustomed to the wearing of glasses, and in the preliminary stage of the experiment plano spectacles were used to which the size lens was later attached.

EXPERIMENTAL RESULTS AND COMMENT

A. *The Effect of Wearing a Meridional Size Lens.*—All experiments gave in general the same result. When the size lens was first added the familiar surroundings took on an unusual appearance, showing the typical spatial distortion introduced by a meridional size lens worn at axis 90. This distortion was more marked in near vision than at distance; it was more pronounced when attention was paid to the shape of things and when the observer fixated an object point instead of letting his glance rove. With continued wearing of the lens, the distortion gradually subsided and finally disappeared. During the last few days the lens was worn it was usually impossible for the observer to detect the distortion in familiar surroundings even when he was giving close attention to the position and shape of objects. The time necessary to become accustomed to the lens varied with the strength of the lens but was never longer than three or four days.

It must be noted that the wearing of the lens caused some definite discomfort. Slight headaches and eyestrain were general, as was a feeling of irritability and nervous tension. I regularly had some gastric distress. The 3 observers did not all have symptoms of the same degree, but none could wear the lens without some unpleasant effect. There was pronounced relief when the lens was eventually removed, although the intensity of all symptoms decreased the longer it was worn.

On the whole, all the observers could go about their duties without great inconvenience; the distortions did not interfere materially with the finer tasks of visuomanual coordination, but I felt that I had to avoid the performance of such operative procedures as cataract extractions during the first days I wore the lens.

As far as the ordinary urban surroundings were concerned, the adaptation to the artifically introduced size difference seemed complete. However, when one went out into the fields or onto a hill with high-grown autumn grass, or in general into surroundings with but few rectilinear, perspective factors, the distortion returned immediately. This happened time and again; it happened even on the very last day the lens was worn. This phenomenon is an established fact.

These observations suggest that one is able to become accustomed to artifically introduced image size differences in the sense that objects are seen in their true shape and localized correctly in space as long as there are in the field of view perspective clues in sufficient number and of sufficient intensity to dominate the stereoscopic factors and to permit a reinterpretation of space. But when there are only few and scanty perspective clues in the field of view, the stereoscopic factors become again effective and the distortion recurs.

B. *Quantitative Results with the Horopter Apparatus.*—The information obtained from the quantitative determination of the image size difference during the experiments must now be considered.

The curve of the empiric horopter as determined by the criterion of fronto-parallelism showed that the initial rotational effect produced by the size lens diminished gradually, at first fast and then more slowly, until finally a certain level was reached, beyond which no further decrease in the effectiveness of the lens occurred. As an example, the curve obtained in one experiment is reproduced in figure 5. However, the effectiveness of the lens was never completely lost; the decrease ranged on the average from one fifth to two thirds of the initial effect. The results obtained with the horopter instrument in 10 experiments are summarized in table 1. The first column records the size lens used, the second the initials of the observer, the third the eye in front of which the lens was worn and the fourth the number of days during which the lens was worn. Then follows the immediate effect of addition of the size lens in terms of percentage size difference

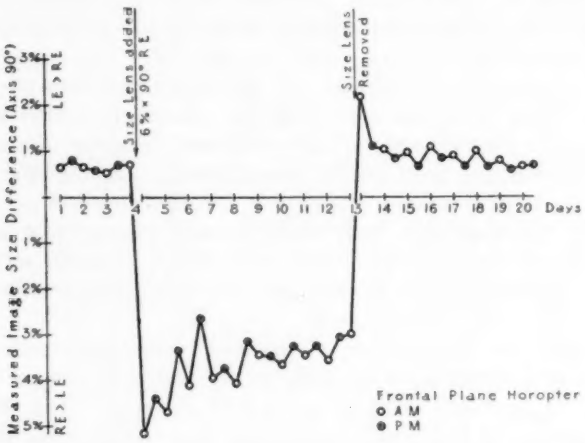

Measured Image Size Difference (Axis 90°)
LE > RE
RE > LE
Size Lens added 6% × 90° RE
Size Lens Removed
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 Days
Frontal Plane Horopter
○ A M
● P M

Fig. 5.—Diagram representing the differences in the size of the images of the two eyes as determined by the criterion of the apparent frontal plane in an experiment in which the observer (R. E. B.) wore a meridional size lens of 6 per cent at axis 90 degrees in front of the right eye.

between the ocular images, and the average decrease in the effectiveness of the lens measured during the last two or three days the lens was worn. In the next column this decrease is expressed in percentage of the initial effect of the size lens. The eighth and ninth columns contain the maximum decrease in a single setting and its amount in percentage of the initial immediate effect of the lens. The tenth column records the effect in percentage size differences measured immediately after the removal of the lens.

This table reveals a number of interesting results. It shows, first of all, that the amount of average and maximum decrease in the effectiveness for different size lenses differs for different observers. But it also shows that the decrease differs with the eye in front of which the lens is worn. Thus, the effect of a size lens of 3 per cent worn by the two observers H. M. B. and R. E. B. in front of the right eye was reduced by about 50 per cent at the end of the experiment, whereas when the lens was worn in front of the left eye the decrease in effectiveness was only about 20 per cent.

This result cannot be fully explained at this time, but it is undoubtedly worthy of further attention. All that can be said is that there is a marked discrepancy in the residual amount of size difference produced by the prolonged wearing of size lenses according to whether the image of the right or the left eye is magnified in the horizontal meridian. Experience has shown that numerous persons when tested at the tilting field [10] or in the leaf room [7] do not respond equally well when size lenses are placed in front of the right and the left eye, respectively. This fact may have some bearing on the problem under consideration, but it cannot explain it, since the 3 observers reacted equally well to size lenses put in front of either eye (fig. 6). It may, however, be assumed that it is possibly easier to overcome the disparity factors and reinterpret the position of objects in space according to the uniocular factors if the image of one eye rather than that of the other is magnified. This may conceivably be connected with the ocular dominance of the subject, and it is to be expected that further research will uncover a relationship between ocular

TABLE 1.—*Average and Maximum Decrease in Effectiveness of Meridional Size Lenses Worn at Axis 90 Degrees in Front of One Eye for a Number of Days as Determined by the Apparent Frontal Plane Horopter Curve*

Size Lens (%)	Observer	Eye Before Which Lens Was Worn	Time During Which Lens Was Worn (Days)	Immediate Effect When Lens Was Added (%)	Average Decrease of Effectiveness of Lens in Percentage Size Difference	Average Decrease of Effectiveness in Percentage of Immediate Effect	Maximum Decrease of Effectiveness of Lens in Percentage Size Difference	Maximum Decrease of Effectiveness of Lens in Percentage of Immediate Effect	Immediate Effect After Removal of Lens
6	H. M. B.	Right	8	5.63	2.51	45	3.79	66	6.69
	R. E. B.	Right	8	5.85	1.88	32	2.18	37	5.10
3	H. M. B.	Right	8	2.44	1.73	70	2.10	86	2.57
	H. M. B.	Right (repeat)	15	2.45	1.02	42	1.49	61	2.99
	H. M. B.	Left	10	2.94	0.55	19	0.81	28	2.79
	R. E. B.	Right	8	2.87	1.45	51	1.78	62	2.60
	R. E. B.	Left	9	2.63	0.59	22	1.02	39	2.86
	M. E. B.*	Right	8	2.76	0.40	15	0.61	22	2.42
	M. E. B.	Right	13	2.54	0.62	24	0.89	35	2.26
1.5	H. M. B.	Right	11	1.30	0.83	64	1.33	100	1.62

* These data were taken with a somewhat different setup of the horopter instrument.

dominance and the response to disparity and perspective factors. But this more intricate question cannot be answered until one knows more about the way in which the adaptation to artificially created size differences takes place.

Since the spatial distortion due to meridional size lenses worn at axis 90 tends to disappear entirely in surroundings offering numerous perspective clues, it was first concluded that the longer the lenses are worn the more the subject learns how to disregard the disparity factors and to reinterpret the surroundings on the basis of the uniocular factors contained in them. The adaptation to the artificially introduced size differences would accordingly be due to a psychologic reinterpretation, not to a physiologic compensation. This explanation, however, does not seem to be borne out by the quantitative experiments. If it were correct, one would not be able to find any compensation in the measurements with the apparent frontal plane horopter, the space eikonometer or the standard eikonometer, since perspective factors are excluded as far as possible from the field of view of these instruments. Yet, as has been shown, there is evidence, even with these instru-

10. Ames, A., Jr.: Aniseikonia: A Factor in the Functioning of Vision, Am. J. Ophth. **18**:1014 (Nov.) 1935.

ments, of a decrease in the effectiveness of the size lenses of from one fifth to two thirds of the initial effect. This would argue in favor of a true physiologic compensatory process, a tipping of the crystalline lens or the like, which would partially offset the artificially introduced size difference.

In trying to understand the nature of the compensation which is apparent in the measurements, one must keep in mind that the adaptation is complete in ordinary surroundings and that the lack of uniocular factors must play some part in this adaptation, since the distortion recurs immediately when there are only a few perspective factors. On the other hand, the perspective factors, although reduced to a minimum, are not entirely excluded in the instruments used. The reinterpretation of spatial relationships which the observer is forced to make while wearing the lenses creates memory values which might well mold to a certain extent the interpretation given to the disparity clues. It stands to reason that an observer who is incessantly exposed to an overwhelming number of uniocular factors in his surroundings will not be able to free himself entirely from their influence during the ten or fifteen minutes which it takes to make the measurements. One can, therefore, assume that the partial compensation evident in the

TABLE 2.—*Difference Between the Settings of the Apparent Frontoparallel Plane in the Morning and in the Evening While Size Lenses Were Worn*

Observer, Eye, Lens	Average Decrease of Effectiveness of Lens in Percentage Size Difference	Average of Morning Settings While Lens Was Worn (%)	Average of Evening Settings While Lens Was Worn (%)	Difference Between Morning and Evening Settings (%)
H. M. B., right, 6%, axis 90	2.51	Right 3.85	Right 2.26	1.59
R. E. B., left, 3%, axis 90	0.59	Left 2.39 (Left 2.68)*	Left 1.75 (Left 1.61)*	0.66 (1.07)*

* The figures in parentheses indicate the average settings and their difference during the first five days of the experiment, during which an occluder was worn in the morning.

measurements with the various instruments is due to the influence of memory values created by the uniocular factors.

There is no actual proof for the correctness of this assumption, but there are some results which seem to support it. One of them is the fact—which has been confirmed by all experiments performed by the 3 observers—that the decrease in effectiveness of the size lens as measured with the three instruments is smallest in the morning and greatest at night. This phenomenon is in itself of considerable interest. It indicates that the essential physiologic binocular cooperation afforded by the disparity factors is more prevalent after sleep, which has to some extent wiped out the memory values created by the uniocular factors. And this, incidentally, throws some light on the essence of sleep as a recuperative process. The difference between the measurements taken in the morning and those taken at night is even more marked when an occluder is worn over one eye from the moment the subject arises until the first measurements are taken. This finding may be of some clinical importance; it suggests that occlusion should be tried in cases in which there is a suspicion that measurements with instruments such as the standard eikonometer do not reveal the full error. But whether or not an occluder is worn, toward the end of the experiments the differences between morning and evening settings level off more and more. Table 2 shows the average of the morning and evening settings in 2 experiments.

The difference between the morning and evening settings could, of course, also be explained by a reversible process of actual physiologic compensation, which

would have to be set in action every morning by binocular stimulation. But there is another observation which strongly supports the reinterpretation theory. While a size lens is worn the first of the five settings of the horopter wires, the average of which constitutes one reading of the apparent frontal plane horopter, frequently shows a greater compensation than the last one. The five apparent frontal plane horopter settings usually do not take more than five to seven minutes, and the differences between the first and last settings can, therefore, not be very pronounced. The measurements on the standard eikonometer and the space eikonometer require as a rule a longer time, and it is significant that the longer the observer looks into the space eikonometer or at the standard eikonometer pattern, the more will the artificially introduced size difference become manifest. Thus, in the case of observer R. E. B., who was wearing a meridional size lens of 3 per cent over the right eye, a quick check with the standard eikonometer and the space eikonometer revealed in the afternoon of the third day of the experiment that the image seen by the right eye was larger by 2 per cent. But after the observer looked into either instrument for about one-half hour the manifest size difference increased to 2.75 per cent for the right eye. Since the observer during all this time was subject to binocular stimulation, it would seem that the increase in the effectiveness of the lens could be attributed only to the fact that the longer an observer watches a field which is relatively free from perspective factors, the more he frees himself of the memory values of the previous experiences and the more he is apt to give weight to the disparity factors.

Another diurnal change warrants a brief mention. When measurements were taken at night, the manifest size difference was frequently larger than in the afternoon. This is apparently a phenomenon of fatigue and would indicate that the uniocular factors are less effective in a fatigued observer than in an unfatigued one. The phenomenon was more apt to occur when the observer had worn a size lens for a number of days, but it did not take place with regularity. Such a regularity would not be expected, since fatigue is not a constant factor. Only one observer (H. M. B.) has more or less regularly determined the horopter curve in the evening hours, and these deductions apply only to his data, but these are quite convincing, as can be seen from the examples in table 3.

There is another factor which one should consider in trying to understand the nature of the adaptation to meridional size lenses. The settings of the apparent frontoparallel plane, based on the disparity factors, show a high degree of accuracy; in fact, the empiric longitudinal horopter has been defined as the locus of maximum stereoscopic sensitivity.[11] Interpretative judgments in spatial localization have a much lower degree of accuracy. One might, therefore, argue that in the case of a physiologic change the mean deviations should not differ essentially, whether or not a lens is worn; a decrease in accuracy would be in favor of an interpretative process. Table 4 shows the average of the mean deviations in millimeters of the spatial longitudinal horopter curves. It can be seen from the figures that the average mean deviations are higher while size lenses are worn by 0.2 mm. for the outer wires and by 0.1 mm. for the inner wires, this fact indicating that the settings are less precise under those circumstances. Since the mean deviations for the outer wires when no size lens is worn are roughly double those for the inner wires, the accuracy of the settings is impaired proportionally over the whole field by about one third. This increase in the mean deviations may be attributable in part to the

11. Tschermak, A.: Optischer Raumsinn, in Bethe, A., and von Bergmann, G.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1931, vol. 12, pt. 2, p. 899.

fact mentioned that the first in a group of five settings often shows a smaller size difference than does the last one when size lenses are worn.

Not only the accuracy of the settings but the response to additional size differences might be affected by a process of compensation for artifically introduced

TABLE 3.—*Examples of Diurnal Changes in the Manifest Size Difference as Determined by the Rotation of the Apparent Frontal Plane Horopter When a Meridional Size Was Worn in Front of One Eye (Observer H. M. B.)*

Size Lens Worn	Day of Experiment	Hour	Size Difference Measured (Right Eye; %)
6%, axis 90°, right eye	First	9:15 a. m.	5.00
		1:15 p. m.	2.74
		11:15 p. m.	2.40
	Third	8:45 a. m.	3.48
		2:15 p. m.	2.52
		10:15 p. m.	2.84
	Sixth	9:00 a. m.	3.52
		2:00 p. m.	2.00
		7:15 p. m.	2.45
3%, axis 90°, right eye	First	8:30 a. m.	2.28
		4:00 p. m.	1.54
		10:00 p. m.	1.12
	Fourth	9:00 a. m.	1.30
		4:00 p. m.	1.06
		10:00 p. m.	1.30
	Seventh	11:00 a. m.	0.84
		6:00 p. m.	1.26
3%, axis 90°, right eye	Second	9:45 a. m.	2.15
		2:30 p. m.	1.57
		6:30 p. m.	1.35
	Third	9:55 a. m.	2.04
		2:30 p. m.	1.25
		11:15 p. m.	1.52
	Fourth	10:00 a. m.	1.85
		4:15 p. m.	1.59
		10:15 p. m.	1.54
	Eighth	8:30 a. m.	1.26
		1:40 p. m.	1.23
		9:20 p. m.	1.44

TABLE 4.—*Summary of Mean Deviations for Experiments Recorded in Table 1*

Observer	Condition	Number of Settings	Lane			
			−8	−4	+4	+8
H. M. B.	Before lens was worn	155	0.60 ± 0.10	0.28 ± 0.03	0.28 ± 0.06	0.54 ± 0.08
	While lens was worn	545	0.79 ± 0.09	0.39 ± 0.03	0.40 ± 0.06	0.74 ± 0.15
	After lens was worn	340	0.61 ± 0.06	0.31 ± 0.04	0.33 ± 0.01	0.63 ± 0.06
R. E. B.	Before lens was worn	125	0.47 ± 0.11	0.26 ± 0.04	0.31 ± 0.06	0.58 ± 0.08
	While lens was worn	365	0.68 ± 0.10	0.37 ± 0.01	0.41 ± 0.06	0.79 ± 0.13
	After lens was worn	200	0.40 ± 0.05	0.22 ± 0.05	0.26 ± 0.06	0.43 ± 0.04
M. E. B.	Before lens was worn	75	0.49 ± 0.08	0.22 ± 0.00	0.23 ± 0.03	0.50 ± 0.10
	While lens was worn	105	0.69 ± 0.10	0.32 ± 0.01	0.25 ± 0.01	0.51 ± 0.09
	After lens was worn	110	0.49 ± 0.05	0.26 ± 0.01	0.29 ± 0.04	0.54 ± 0.04

size differences. This possibility was checked in every experiment, but all observers showed the same geometric effect before, while and after the lens was worn except that the zero position was shifted according to the residual effect of the size lens. In other words, their sensitivity to disparate stimulations as determined by their response to artificial meridional image size differences of from 1 to 4 per cent was not impaired by their wearing a meridional size lens, as can be seen from figure 6.

The slopes [12] were determined for all horopter curves taken during the experiments. There is a tendency for the curves to be steeper when size lenses are worn; in all but 2 of the experiments reported in table 1 the average slope was higher during the experiment than before and after. The average increase of the slopes for all experiments of observer H. M. B. was 0.11 and for those of observer R. E. B. 0.15; for observer M. E. B. the average increase was zero. The increase would indicate a change in shape of the horopter curve in the direction of less concavity (increase in the Hering-Hillebrand deviation; the curve tends to approach the objective frontoparallel plane) under the influence of prolonged wearing of meridional size lenses, but this is a trend rather than a definite occurrence.

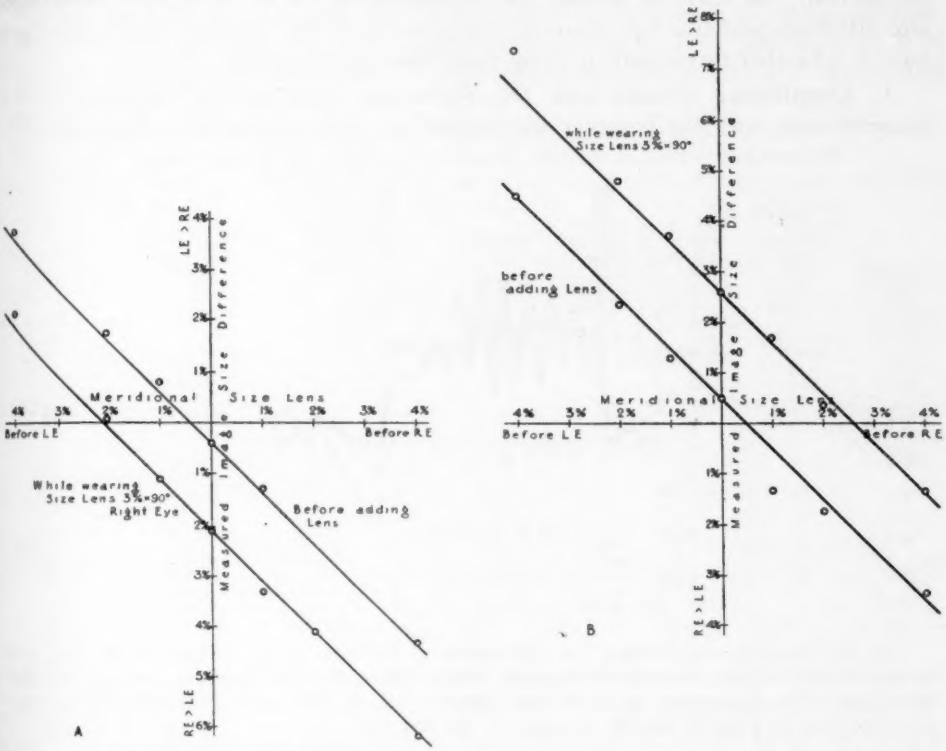


Fig. 6.—Sensitivity to meridional size lenses placed in front of each eye before and while a size lens was worn. The abscissa indicates the lens placed in front of the eyes; the ordinate, the response (the resulting image size difference) as determined by the criterion of the apparent frontoparallel plane. *A*, data of observer M. E. B.; *B*, data of observer R. E. B.

While the setting of the apparent frontoparallel plane by means of the wires of the horopter apparatus is to a certain extent subject to the influence of perspective factors, any direct influence of these factors is excluded when the nonius horopter is used. This is due to the fact that an entirely different criterion is used and that the settings are independent of the position of the wires relative to each other

12. The slope of the horopter curve, derived from the analytic transformation of the spatial curve, is a measure of the deviation of the entire horopter curve from the Vieth-Müller circle and, therefore, a measure for the Hering-Hillebrand deviation of the horopter curve.[4] When the slope is zero, the horopter curve coincides with the Vieth-Müller circle; when positive it deviates in the direction of the objective frontoparallel plane.

and to the fixation wire. The behavior of the nonius horopter would be, therefore, of some importance with regard to the question under discussion. However, the nonius horopter settings are extremely difficult and are vitiated by certain other factors. So far only 1 of the observers (H. M. B.) has made preliminary studies with this method, and these have shown that for him in general the nonius horopter readings indicate a much larger image size difference than the readings with the apparent frontal plane method and, furthermore, that by this method no loss of effectiveness seems to be apparent when a meridional size lens is worn. The first fact if borne out by further studies would imply that this method permits one to determine the full size difference present, which is otherwise partly masked; the second, that there is actually no compensation for an artificially introduced size difference and that the apparent compensation is due to other than physiologic factors. Further investigations along these lines are necessary.

C. *Quantitative Results with the Space and Standard Eikonometers.*—The measurements with the horopter instrument give information only about size dif-

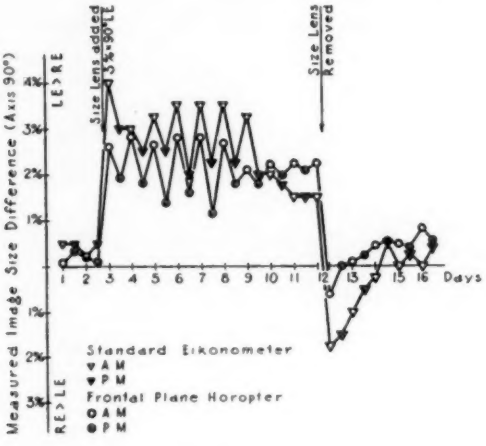


Fig. 7.—Diagram representing the differences in the size of the images of the two eyes as determined by the standard eikonometer (near vision, axis 90 degrees) and the horopter apparatus in an experiment in which the observer (R. E. B.) wore a meridional size lens of 3 per cent at axis 90 degrees in front of the left eye.

ferences in the horizontal meridian. There is the possibility that during the time the lenses are worn some changes might occur in the vertical and oblique meridians which would explain the reduced effectiveness in the horizontal meridian. In order to investigate this possibility measurements were made with the space eikonometer and the standard eikonometer.

These measurements showed that there was no change whatever in the vertical and oblique meridians; the measurements remained the same throughout the experiment. No transformation of the horizontal into vertical or oblique size differences took place, but a decrease in the effectiveness of the size lens was found similar to that with the horopter apparatus. Figure 7 shows an example of the curves resulting from 1 experiment.

A comparison of the results obtained with the various instruments is of interest. Some of these results are summarized in table 5. As can be seen from these data, the trend is the same with all three instruments. If anything, the

measured decrease in the response to the size lens in the horizontal meridian was higher with the space and standard eikonometers, especially for observer R. E. B.

In view of the different bases of the three methods it was of interest to correlate the measurements obtained with the three instruments. While one is making horopter settings, fixation is strictly maintained; in the space eikonometer a similar criterion as in the horopter instrument is used, but the observer's gaze is not fixed; in the standard eikonometer the observer has to move his eyes 4 degrees from the fixation point up, down and sideways, and an altogether different criterion is used in the determination of the image size difference. The data obtained in all experiments were correlated, but I shall report here as an example only the figures for the data of observer R. E. B., for which the scatter diagrams are given in figure 8. The Pearson correlation coefficient was high when all data were taken into account; the horopter and space eikonometer measurements at axis 90 correlated by 0.92, and the horopter and the standard eikonometer measurements at axis 90 by 0.98.

TABLE 5.—*Comparison of Results Obtained in 3 Experiments with the Apparent Frontal Plane Horopter, the Space Eikonometer and the Standard Eikonometer*

Observer, Eye, Lens	Instrument	Immediate Effect of Addition of Size Lens (%)	Average Decrease in Effectiveness of Size Lens in Percentage Size Difference	Average Decrease in Effectiveness of Size Lens in Percentage of Immediate Effect (%)	Lowest Single Reading While Lens Was Worn in Percentage Size Difference	Maximum Decrease in Effectiveness of Size Lens in Percentage of Immediate Effect	Immediate Effect After Removal of Size Lens
H. M. B.; 3%, axis 90°; right eye	Horopter.....	2.45	1.02	42	1.49	61	2.99
	Space eikonometer, axis 90°.....	2.94	1.37	47	2.10	71	3.16
M. E. B.; 3%, axis 90°; right eye	Horopter.....	2.54	0.62	24	0.89	35	2.26
	Space eikonometer, axis 90°.....	3.07	0.61	20	0.74	24	2.47
R. E. B.; 3%, axis 90°; left eye	Horopter.....	2.63	0.59	23	1.26	48	2.86
	Space eikonometer, axis 90°.....	2.88	1.08	38	1.35	47	2.87
	Standard eikonometer, axis 90°.....	3.25	1.50	46	2.25	69	3.75

However, when the data obtained while lenses were worn and after they were removed were considered separately, the picture was somewhat different. The correlation coefficient for the horopter measurements and the standard eikonometer measurements at distant vision was 0.80 after the removal of a 6 per cent size lens and 0.93 after the removal of a 3 per cent size lens. The data obtained while these lenses were worn showed a poor correlation, viz., 0.53 and 0.49, respectively. The generally high correlation of the measurements with the three instruments is further proof that all three measure the same thing: the difference in the size of the images of the two eyes. The low correlation of the measurements when lenses are worn can be considered as supporting evidence that the partial loss of effectiveness of the size lenses evident in the measurements is due to psychologic factors.

D. *Quantitative Results with the Rotating Plane Instrument.*—Instead of keeping the field of view of the observer as free as possible from perspective factors, one may deliberately add such factors to the field in order to determine their effect on the measurements. This would be an attempt to reproduce to a certain controlled extent the natural conditions of seeing and at the same time make a quantitative determination possible. To achieve this, the rotating plane instrument was used. The patterns employed were (*a*) five vertical lines the ends of which were seen by

the observer, (*b*) five vertical lines connected by a horizontal line at the top and at the bottom, (*c*) a large rectangle and (*d*) a large oval.

The settings with this method proved to be both difficult to make and difficult to interpret. Instead of appearing to rotate, or while appearing to rotate, the pattern frequently changed its shape and the observer was induced to set the cardboard not according to the criterion of frontoparallelism but according to the shape of the

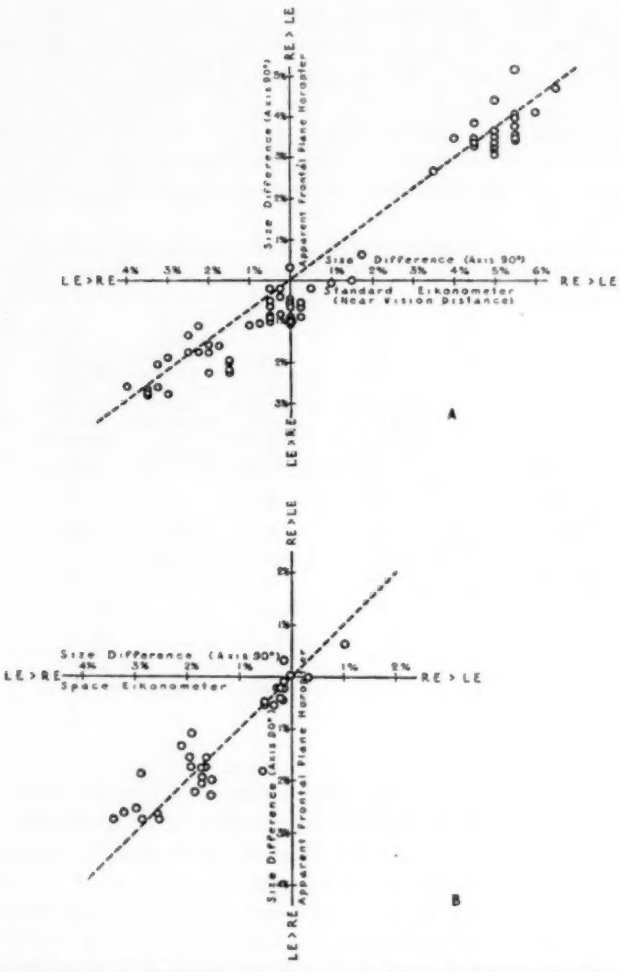


Fig. 8.—*A*, scatter diagram showing correlation of data obtained with the horopter apparatus and the standard eikonometer (near vision, axis 90 degrees). Data of R. E. B.

B, scatter diagram showing correlation of data obtained with the horopter apparatus and the space eikonometer (axis 90 degrees). Data of R. E. B.

elements of the pattern. The observer could never be quite sure that he was setting the cardboard consistently according to one or the other criterion, especially since the cardboard (the background) appeared sometimes to be in a plane different from the pattern itself. Theoretically, the arrangement raised a number of questions, such as the influence of form on frontoparallel settings, which are outside the scope of this paper. The results will, therefore, be reported only in so far as they have a bearing on the problem under discussion.

Preliminary experiments showed that there is a remarkable individual difference in the response to size lenses when patterns containing perspective elements are used as test objects. Some observers show little if any rotation; others respond more or less fully to the size lenses (figs. 9 and 10). The explanation for this is that some persons give more weight to the disparity factors, while the visual act of others is dominated by the uniocular factors. It might actually be

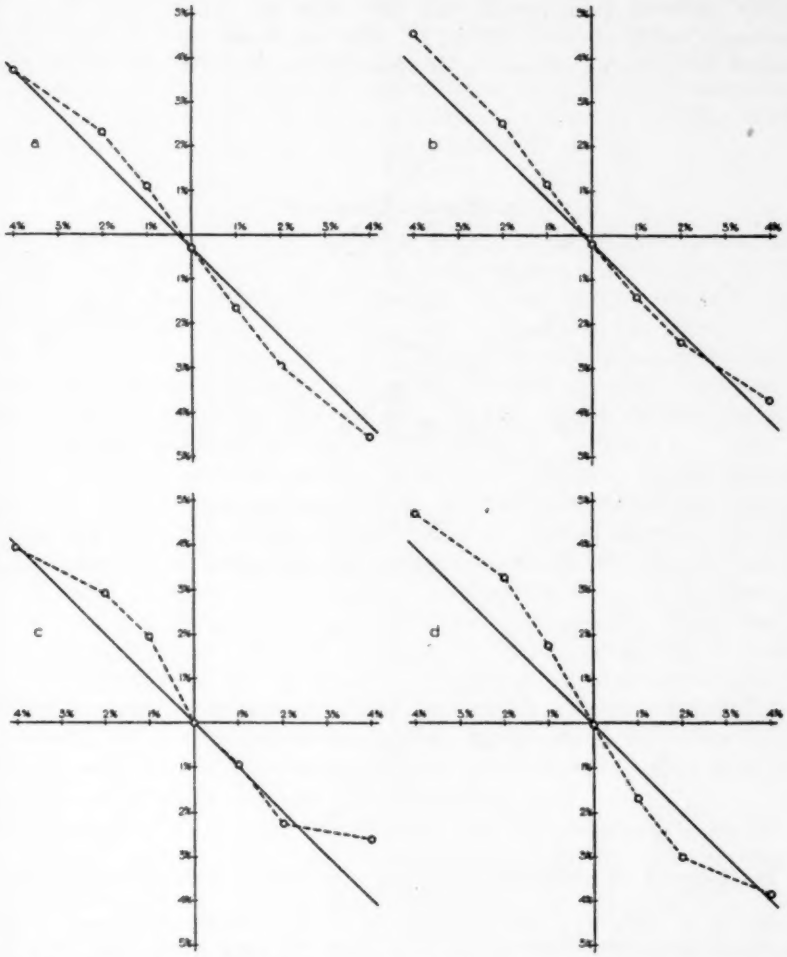


Fig. 9.—Response to artificially introduced size differences when perspective patterns were used. The abscissa indicates the size lens placed in front of the right eye (right half) or left eye (left half); the ordinate indicates the observer's response as determined by the rotation of the plane of the pattern. The patterns used were five vertical lines the end of which were seen by the observer: (*a*), five vertical lines connected by a horizontal line at the top and at the bottom; (*b*), a large rectangle (*c*) and a large oval (*d*). This observer (M. E. B.) showed a satisfactory sensitivity to meridional size lenses for most patterns.

possible to establish on this basis a typology of visual characters, and the result is, therefore, of broad general significance. Among the observers who wore size lenses the two extremes are represented by R. E. B., who showed little or no response to the size lenses when the patterns were used, and M. E. B., who responded as a

rule quite fully. The latter observer had the least tendency to show a decrease in the effectiveness of the size lenses, and it is possible that there is a causal relation between these two facts. It must also be mentioned that the different observers not only demonstrated individual differences in their sensitivity to size lenses when patterns were used but reacted differently at different times.

As to the result of the measurements with the rotating plane apparatus while size lenses were worn, observer R. E. B., who did not respond in the test with the perspective patterns consequently did not show any appreciable change in the measurements, while observer M. E. B., who responded more or less fully to size lenses with the patterns, showed a decrease in the effectiveness of the size lenses

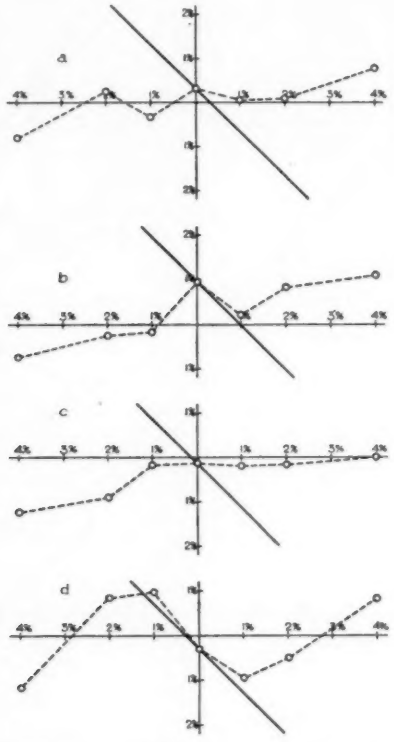


Fig. 10.—Response to artificially introduced size differences when perspective patterns were used. The significance of the abscissa and ordinate is the same as in figure 9, as are the patterns (*a*, *b*, *c* and *d*). This observer (R. E. B.) showed no response to meridional size lenses with any of the patterns.

worn which was about one-third greater than in the measurements with the horopter instrument.

E. *Effect of Removal of Size Lens.*—The last experimental result which must be discussed is the effect produced by the removal of the size lens. As soon as the lens is removed, a considerable tilting of objects in space is noted *in the direction opposite to the one which occurs when the lens is first added.* In other words, the removal of the size lens from the right eye if the lens has been worn for some time acts as if a meridional size lens at axis 90 had been added to the left eye. This distortion not only is noticeable in the normal environment but is evident in a rotation of the horopter curve and in the measurements with the space eikonometer

and standard eikonometer. The return to the normal condition is comparable to the process which takes place when the observer becomes accustomed to the added size lens. The effect lingers for some time—for from one to three days—in the usual surroundings and is again more marked in an environment lacking in uniocular factors, but it decreases more rapidly than when a size lens is added and worn. However, in the measurements with the various instruments a residual effect can often be demonstrated a week or ten days after the removal of the lens.

It is again impossible to tell with certainty whether the process which takes place after the removal of the lens is due to a physiologic change or to a psychologic reinterpretation, but it is evident that the wearing of a meridional size lens creates a new equilibrium which is not immediately replaced by the normal equilibrium. The normal condition has to be reacquired by a process similar to the one which created the equilibrium when the lens was worn.

CONCLUSIONS

The evidence presented in the foregoing pages can be summarized as follows:

When a person with normal binocular vision places a meridional size lens at axis 90 in front of one eye and wears this lens for several days, he at first experiences a typical distortion of his surroundings. The longer the lens is worn, the less the distortion is noticeable, and it finally disappears and is absent as long as the observer remains within surroundings abundant in perspective and other uniocular elements. There is, apparently, a complete adaptation to the distortion created by the lens in normal surroundings.

However, if the number of effective perspective factors in the surroundings is negligible, the distortion recurs immediately, and measurements made with instruments from whose field of view these factors are absent show that the larger part of the image size difference is still present, no matter how long the size lens is worn. But there is an average decrease in the effectiveness of the size lens of from one fifth to two thirds as measured with these instruments. This decrease in effectiveness could be due either to a process of actual physiologic compensation, leading to a redistribution of the stimuli on the retinas, or to a psychologic reinterpretation of the relation of objects in space under the influence of uniocular clues in the surroundings and of memory values of past experience. There is no conclusive proof for either theory, but the weight of the evidence seems to be in favor of a reinterpretation rather than of a compensation.

Certain observations made in the course of the experiments give an interesting insight into the relation between the disparity factors and the uniocular factors in the act of vision. It has, of course, long been known that the uniocular factors and the memory values of past experience mold to a large extent the interpretation given to the clues arising from the stimulation of disparate retinal elements.[13] But the developments in the research on aniseikonia and especially the construction of the size lenses which produce a magnification without causing a refractive change provide means by which this interrelation can be far better investigated than was heretofore possible.

The experiments with artificially introduced meridional size differences confirm the well known fact that the disparity factors are the more fundamental ones. Yet

13. "Any one who knows how pliable our spatial visual perceptions are under the influence of various conditions of observation and under the influence of past experience, taken into account consciously or unconsciously, should not be surprised at the multiplicity of results of observations on different objects and with different observers." (Erggellet: Brillenlehre, in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1932, vol. 2, p. 805.)

they also show that the disparity factors can be largely disregarded when abundant perspective factors are present in a person's surroundings, but that they become immediately operative when the perspective factors are scanty. Fatigue seems to reduce the faculty to disregard the disparity factors, and sleep apparently wipes out to some extent the recent memory values created by a reinterpretation of the relation of objects in space.

Two further conclusions of broad significance are suggested by the experiments. One is based on the fact that it makes a difference in the decrease in effectiveness of the size lenses whether the image of the right or the left eye is magnified in the horizontal meridian. At first this result is rather startling; one would not expect such a difference, since the effect of aniseikonia on spatial localization depends solely on the ratio of the sizes of the two ocular images. But since such a difference was found to be an experimental fact, it must be assumed that different "weight" is given to the two eyes with respect to the response to disparity and uniocular clues. This difference in reaction may have some connection with the ocular dominance.

The second conclusion is closely related to the first and concerns individual differences in the response to disparity and uniocular factors. Some persons with normal binocular vision are more apt to let the uniocular factors influence the spatial localization derived from disparity clues than others, in whom the disparity clues dominate. The latter persons seem to be the ones whose ocular condition shows the least deviation from the normal. It may be possible to establish a typology of visual characters on the basis of the response to the uniocular and binocular factors.

The results of the experiments also have some bearing on the explanation of the metamorphopsias and their gradual disappearance. Wilhelm Wundt [14] discussed his own case of disseminated choroiditis of the right eye, which affected the region of the posterior pole of the eye but spared the fovea itself. At first he noticed a pronounced metamorphopsia, which disappeared gradually, leaving only minor irregular distortions at the edge of the diseased area near the macula. Wundt also mentioned the metamorphopsia introduced by prisms and quoted O. Schwarz, who stated:

> In a case in which prismatic glasses base out were given for so-called dynamic convergence, an interesting fact was noted. After the glasses were worn for a while, the distortions, noticed at first, disappeared. Yet as the glasses were removed, they reappeared, but in a direction opposite to the one experienced previously; these distortions also disappeared after a while.[15]

Wundt considered the disappearance of the metamorphopsias to be a proof of the empiristic theory of spatial localization. He argued that the retinal elements dislodged by the disease of his right eye could not have returned to their exact original position after the disease had healed and scars had formed. Only an acquired change in the relative visual directions could, in his opinion, explain the disappearance of the metamorphopsia. Similar deductions would apply to the distortions produced by prisms, especially in view of the fact, justly emphasized by Wundt, that distortions opposite in direction to the original ones occur when the prisms are removed.

But one does not have to resort to such a sweeping conclusion as a change in the innate relative visual directions of the retinal elements to explain the

14. Wundt, W.: Zur Theorie der räumlichen Gesichtswahrnehmungen, Philosophische Studien, Leipzig, W. Engelmann, 1898, vol. 14, p. 1.

15. James J. Gibson (Gibson, J. J.: Adaptation, After-Effect and Contrast in the Perception of Curved Lines, J. Exper. Psychol. **16**:1 [Feb.] 1933) reports experiments along the same lines.

phenomena. The experiments in which a meridional size lens was worn which at first produced distortions analogous to the ones described by Wundt clearly indicate that no change in the relative visual directions of the retinal elements takes place, since the distortions can be shown to be always present in appropriate surroundings, although they disappear completely under ordinary circumstances. The complete disappearance of the metamorphopsias, like the disappearance of the distortions introduced by meridional size lenses, can be fully explained on the basis of a reinterpretation of the relation of objects in space under the influence of uniocular factors. This is a process of learning but a very different one from that which Wundt had in mind. In fact, the results reported in this paper not only demonstrate the relative importance of and the part played by the disparity factors and the uniocular factors in spatial orientation but open up a possibility for a direct experimental check on the validity of the nativistic theory of space perception.

It may now be attempted to answer the questions raised with regard to spontaneous aniseikonia in the introductory chapter of this paper. Why is it that complaints about disturbances of spatial localization on the part of patients with aniseikonia are extremely rare, in spite of the fact that aniseikonia always entails a disturbance of space perception? How, then, does aniseikonia affect a person's functioning within space?

From the experiments reported in this paper it may be inferred that patients with aniseikonia handle the distortions which necessarily arise from their condition in the same way in which the observers handled the artificially introduced meridional size difference. They disregard largely the disparity factors and rely on the perspective clues. But they have not actually compensated for their aniseikonia, or at least have compensated for only a fraction of it. Nor have the relative visual directions of the retinal elements undergone any change. Because as soon as the patients are placed in artificial or in natural surroundings in which there is a minimum of uniocular factors the distortion of the relation of objects in space characteristic of the type of aniseikonia which the patients have becomes at once apparent.[7] Aniseikonia is in this respect, as in many others, comparable to the heterophorias in that its spatial effects remain latent in ordinary surroundings but become manifest under appropriate conditions, just as the heterophorias become manifest only after fusion is suspended. A person with aniseikonia will have no trouble in ordinary surroundings; but under certain special conditions, and especially when tired, he may experience considerable disturbance in proper functioning in space.

Similar considerations apply to the remark which is sometimes heard that it is superfluous to correct aniseikonic defects, since most people can get accustomed to even larger differences in the size of the ocular images than are currently corrected by iseikonic lenses.

It is, indeed, well known that all spectacles, while achieving the main purpose of providing optimum vision for distance, introduce at the same time a number of radical changes in the visual act of the wearer. Not only is the size of the retinal images changed, as compared with that of the emmetropic eye or with the (sharp or blurred) image the wearer had previous to the correction of his refractive error. The directions in which object points appear in indirect vision are also changed, and with them the field of vision and perspective, so that the size of the objects as well as the interpretation of spatial relations must necessarily be different with and without spectacles. The accessory effects of spectacles on spatial orientation are more pronounced when there is even a small difference in the refractive condition of the two eyes, especially a difference in the astigmatic

error.[18] The result is an unusual, often distorted, appearance of the environment when new spectacles are first put on; but soon the wearer becomes accustomed to his glasses and the appearance of his environment returns to normal. This process of adaptation, also, is one not of compensation but only of reinterpretation, since it can be shown with instruments such as the space eikonometer that an incorrect spatial localization introduced by the spectacles will persist no matter how long the glasses are worn. The correct spatial orientation achieved with iseikonic lenses would in itself justify their use, even if it were not for other indications for their clinical application.

SUMMARY

Experiments are reported in which 3 observers wore a meridional size lens at axis 90 in front of one eye for eight to fourteen days.

While they were wearing the lens definite discomfort (eyestrain, nervous tension, etc.) was experienced by the observers.

At first the size lens caused the typical disturbance in spatial orientation which would be expected from such a lens, but this disturbance gradually diminished until the usual surroundings, abundant in uniocular clues, assumed a normal appearance.

However, even after this adaptation had taken place, the disturbance in spatial orientation became immediately manifest when the observer was placed in surroundings lacking in uniocular clues, and quantitative determinations with instruments such as the horopter apparatus and the standard and space eikonometers always showed the greater part of the image size difference to be present.

But after the lens was worn for some time there became manifest a decrease in the amount of the measured image size difference ranging from one fifth to two thirds. The amount of the decrease varied with the person and with the eye in front of which the size lens was worn. There also were certain diurnal variations. The sensitivity to additional size lenses at axis 90 was not influenced by the wearing of the lens.

The question as to the nature of the decrease in the measured image size difference is brought up. The experimental evidence in favor of each of the two possible explanations—psychologic adaptation and physiologic compensation—is discussed.

Measurements made with an instrument with a rotating frontal plane showed a marked difference between different observers in the response to size lenses when perspective patterns were used. This difference permits a classification of subjects according to whether they give more weight to uniocular or to binocular factors in their field of view. It would appear that the better a subject's binocular cooperation the more he is likely to respond to disparity factors.

The implications of the results obtained are discussed with regard to the theory of space perception and with regard to the metamorphopsias.

The results of the experimental investigation are applied to the question as to how patients with spontaneous, clinically significant aniseikonia deal with spatial orientation. It is pointed out that such patients may more or less completely adapt themselves to the disturbance in spatial orientation in ordinary surroundings abundant in uniocular factors. However, they cannot actually compensate for their image size difference, or at least can compensate only for a fraction of it.

Prof. Adelbert Ames Jr. and Prof. Kenneth N. Ogle advised in this work, and Mr. Robert E. Bannon and Mrs. Mary Beebe acted as observers.

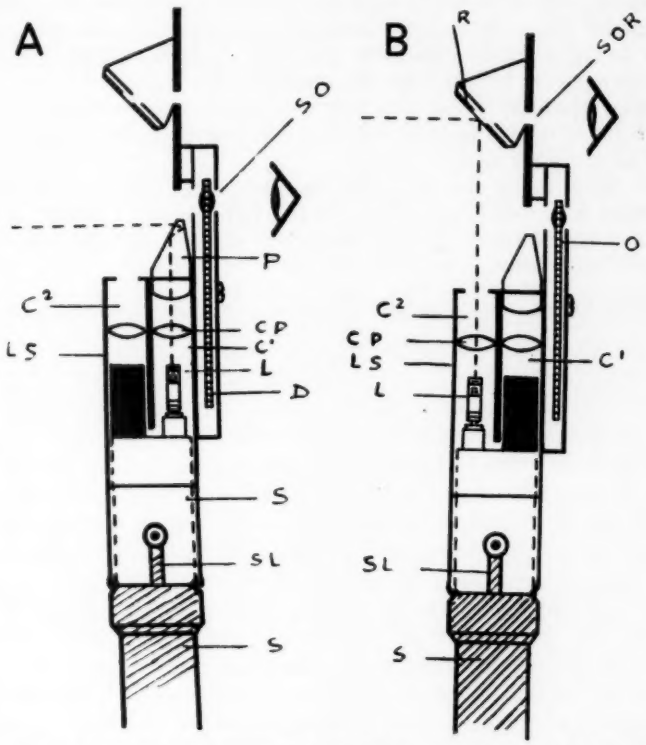
Dartmouth Eye Institute.

Clinical Notes

A COMBINED OPHTHALMOSCOPE AND RETINOSCOPE

MAJOR LOUIS K. PITMAN, MEDICAL CORPS, ARMY OF THE UNITED STATES

The May electric ophthalmoscope is the instrument most generally used. The light, derived from a lamp with a loop or a curled filament, is fixed on the end of a stem projecting from a battery handle. The tube of the head of the ophthalmoscope, within which this stem is adjustably mounted, holds a condensing lens and a reflecting prism. This lens and prism project the light from the lamp into the



A, ophthalmoscope, and *B*, retinoscope. *L* is the lamp, which is in the posterior chamber, C^1, in *A* and in the anterior chamber, C^2, in *B*; *CP*, the condensing lens; *D*, the dial frame holding the lenses; *LS*, the tube; *P*, the reflecting prism; *R*, the reflecting surface; *S*, the stem; *SL*, the slit; *SO*, the sight opening for the ophthalmoscope, and *SOR*, the sight opening for the retinoscope.

eye. Behind the reflecting mechanism is a lens disk provided with a series of lenses, concave and convex, which follow each other in regular order from weaker to stronger. Each lens can be placed in the sight opening, located above the level of the reflector, by manipulating the milled edge of the disk. Opposite each lens is an illuminated number, indicating its strength in diopters.

From the Station Hospital, Eye, Ear, Nose and Throat Service, Basic Training Center no. 10, Army Air Force Technical Training Command, Colonel Robert J. Platt, Commanding Officer.

The electric retinoscope has a lamp mounted on a stem similar to that of the ophthalmoscope. The stem is adjustably mounted within the tube of the retinoscope head. The light rays pass through a condensing lens toward a plane or a concave reflecting surface having a sight opening in the center. The light is thrown into the eye at a distance of 1 meter.

An efficient unit head combining the ophthalmoscope and the retinoscope will eliminate an extra instrument, with saving of material and lowering of the cost of the instrument.

The accompanying schematic drawing shows a cross section of a combined ophthalmoscope and retinoscope head. The tube, *LS,* of the unit head is divided into compartments, C^1 and C^2, each holding a condensing lens, *CP*. The stem, *S,* carrying the lamp, is bifurcated at its end. One stem of the bifurcation carries the lamp, *L,* while the other stem is blank (black). There are two opposite slits, *SL,* in the wall of the tube. The stem, *S,* carries a set screw at its side. When the stem, *S,* is mounted within the tube and the set screw is passed through one slit, the lamp will be brought into the posterior chamber, C^1 (figure *A*). In order to bring the lamp, *L,* into the anterior chamber, C^2, the stem is drawn out, the set screw being released from the slit, and is then rotated 180 degrees; this permits the screw to be locked into the opposite slit.

The posterior chamber fulfils the function of the ophthalmoscope, for the light passes through the condensing lens and the reflecting prism into the eye (figure *A*). The sight opening *SO* is used.

When the lamp is in the anterior chamber, the retinoscope portion of the instrument comes into use (figure *B*), for the light passes through the condensing lens, *CP,* toward the plane or concave reflecting surface, *R,* and into the eye. The sight opening *SOR* is used.

Basic Training Center, no. 10, Army Air Force, Technical Training Command, Greensboro, N. C.

Ophthalmologic Reviews

EDITED BY DR. FRANCIS HEED ADLER

VISUAL IMPAIRMENT DURING TRYPARSAMIDE THERAPY

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In the second year after the synthesis of tryparsamide had been accomplished, Pearce and Brown [1] noted experimentally that the therapeutic use of the drug was not associated with organic or functional disturbance and, further, that "a definite effect was produced upon the course of the Treponema infection due to the peculiar manner in which the drug modified or controlled the infection." In 1924 these investigators [2] further characterized tryparsamide as having "comparative freedom of untoward effect, moderate treponemacidal action, high tissue penetrability, and the ability to reinforce the powers of natural resistance." Tryparsamide is firmly established as an essential modern agent in the therapy of neurosyphilis, and at least certain of these early noted factors have been substantiated by the clinical experience of the intervening period. With regard to the visual aspects of tryparsamide therapy, however, there has been a persistent lack of accord in opinion. When Lorenz and associates [3] introduced tryparsamide into the clinical treatment of neurosyphilis in 1923 admonition was made that damage to the visual system might be associated with its use. Since that time the deleterious effect of tryparsamide on the visual system has been the subject of intensive clinical and experimental observation and controversy, as represented by a voluminous literature comprehending separate phases of the problem. Elucidation of the process, the character and the frequency of untoward visual effects of tryparsamide has remained incomplete, as have satisfactory criteria regarding the ocular contraindications to therapy with the drug in neurosyphilis. The formulation of such criteria, requiring the satisfactory correlation of the factors of altered physiology of vision, pathologic changes in the optic nerve and virulence of the infection, and evaluation of the toxicity of and idiosyncrasy to the drug are complicated by the inadequacy or inaccessibility of much clinical and pathologic material. It is an unfortunate fact that many of the largest statistical collections and clinicoanalytic summaries presenting data derived from the use of tryparsamide refer satisfactorily only to the effect of the drug on neurosyphilis; by even lenient standards, adequate data regarding ocular conditions prior to, coincident with and subsequent to this type of therapy are frequently absent, owing, certainly, to the unexpectedness of many visual reactions, the occult and delayed character of other types of visual involvement, the similarity of syphilitic and tryparsamide-produced effects and the difficulties inherent in detailed and prolonged routine observation by both the ophthalmologist and the syphilologist. As indication of the diversity of opinion, the reports of

1. Pearce, L., and Brown, W. H.: Chemotherapy of Trypanosome and Spirochaete Infections, J. Exper. Med. **30**:417, 455 and 483, 1919.

2. Brown, W. H., and Pearce, L.: Tryparsamide: Its Actions and Uses, J. A. M. A. **82**:5 (Jan. 5) 1924.

3. Lorenz, W. F.; Loevenhart, A. S.; Bleckwenn, W. J., and Hodges, F. J.: Therapeutic Use of Tryparsamide in Neurosyphilis, J. A. M. A. **80**:1497 (May 26) 1923.

Tennent [4] (50 cases), Hyder [5] (22 cases), Dawson [6] (20 cases), Lichtenstein [7] (76 cases), Wolfsohn and Leiva [8] (37 cases) and Skoog [9] (50 cases) provide little evidence that use of tryparsamide is a threat to the visual system, while Bleumel and Grieg [10] noted disastrous results in 10 of 50 cases and characterized the drug as "therapeutic dynamite."

Sutherland-Campbell [11] has summarized the ocular problem of the use of tryparsamide as follows:

> This vacillation in the condemnation and advocacy of a drug is to be expected in view of the fact that tryparsamide is generally conceded to be the most efficacious drug used in the therapy of generalized neurosyphilis, while little is known concerning the mechanism of the production of amblyopia as induced either by syphilis or by the pentavalent arsenical.

The ocular problems associated with tryparsamide therapy lend themselves to general outline as follows: first, the ocular effects of tryparsamide when preexisting syphilitic disease of the optic nerve is present; second, the designation of lesions according to whether the damage to the retina or optic nerve is primarily the result of syphilis, of therapy with tryparsamide or of factors introduced by the use of tryparsamide during a period of inactive or active involvement of the optic nerve in a syphilitic process (Jarisch-Herxheimer reaction); third, evaluation of objective and subjective findings with regard to modification of tryparsamide therapy; fourth, evaluation of factors of individual doses, number of injections and subsequent series of injections; fifth, the nature of the reaction to tryparsamide from the visual aspect, and, sixth, the nature of the tryparsamide reaction from the pathologic aspect.

THE DRUG

Tryparsamide is the sodium salt of *N*-phenylglycinamide-*p*-arsonic acid. Synthesized in 1917 by Jacobs and Heidelberger,[12] of the Rockefeller Institute, it is a white crystalline powder, 1 Gm. of which will dissolve in 1 cc. of water to produce an alkaline solution. The arsenic content in the pentavalent form is 25.32 per cent. The drug is of extremely low toxicity when given by intravenous or intramuscular injection; its clinical use is frequently associated with a systemic tonic or mild stimulant effect.

Voegtlin, Smith, Dyer and Thompson [13] demonstrated experimentally that tryparsamide penetrates into the tissues of the central nervous system. Fordyce and Myers [14] could not demonstrate such unusual penetrative power; examination

4. Tennent, T.: Investigations into the Prolonged Treatment of General Paralysis with Tryparsamide, J. Ment. Sc. **77**:86, 1931.

5. Hyder, H. P.: Tryparsamide in Neurosyphilis, M. J. & Rec. **121**:475, 1925.

6. Dawson, W. S.: Treatment of General Paralysis and Tabes by Tryparsamide, Lancet **1**:1072, 1925.

7. Lichtenstein, J. V.: Tryparsamide Therapy, Arch. Dermat. & Syph. **24**:182 (Aug.) 1931.

8. Wolfsohn, J. M., and Leiva, C.: Clinical and Serologic Studies of Neurosyphilis with Tryparsamide Therapy, J. A. M. A. **85**:494 (Aug. 15) 1925.

9. Skoog, A. L.: Tryparsamide Therapy in Neurosyphilis, J. Missouri M. A. **22**:387, 1925.

10. Bleumel, C. S., and Grieg, W. M.: Results Obtained with Tryparsamide in Fifty Cases of Neurosyphilis, Colorado Med. **22**:16, 1925.

11. Sutherland-Campbell, H.: Value of Tryparsamide in Treatment of Atrophy of Optic Nerve Due to Syphilis, Arch. Ophth. **24**:670 (Oct.) 1940.

12. Jacobs, W. A., and Heidelberger, M.: Aromatic Arsenic Compounds, J. Am. Chem. Soc. **41**:1581, 1917.

13. Voegtlin, C.; Smith, M. I.; Dyer, H., and Thompson, J. W.: Penetration of Arsenic in Cerebrospinal Fluid, Pub. Health Rep. **38**:1003, 1923.

14. Fordyce, J. A., and Myers, C. N.: Quantitative Studies in Syphilis from a Clinical and Biological Point of View, Am. J. Syph. **9**:490, 1925.

of the spinal fluid of patients receiving a routine type of tryparsamide therapy showed the complete absence of arsenic in 14 per cent. In other patients the amount of arsenic did not exceed that obtaining in treatment with other arsenical preparations. In order to obtain a level of arsenic in the cerebrospinal fluid comparable to that of silver arsphenamine, it was necessary to introduce seven and one-half times as much tryparsamide. Further, they noted that owing to the rapid excretion of tryparsamide the amount of arsenic available for penetration after the expiration of twenty-four hours was practically negligible. It is their conclusion that therapeutic penetration is hypothetic in that other factors may be involved. Cornwall, Bunker and Myers [15] determined that the maximum amount of arsenic recoverable from the spinal fluid after therapeutic administration of tryparsamide was 7.8 mg. per hundred grams. This amount was comparable to that noted for arsphenamine and for neoarsphenamine but was considerably less than that obtained in silver arsphenamine therapy. It was suggested that the favorable clinical results that have been reported in neurosyphilis as a result of treatment with tryparsamide must be ascribed to factors other than the actual quantity of arsenic that enters the spinal fluid.

Basing their conclusion on their clinical experience with tryparsamide, and recognizing the low treponemacidal action of tryparsamide as compared with the arsphenamines, Moore, Robinson and Lyman [16] stated in 1924 that the use of tryparsamide in the treatment of syphilitic states other than neurosyphilis was precluded, a view more recently substantiated and applied to the clinical use of the drug.[17]

Moore [17a] outlined the clinical use of tryparsamide in neurosyphilis as follows: The drug is contraindicated except in the treatment of neurosyphilis, for which it is usually used after six months of preliminary treatment with arsphenamine. The average, and the maximum, dose is 3 Gm. given intravenously, although there may be some advantage in the use of an initial dose of 1 Gm. the first week, 2 Gm. the second week and 3 Gm. each succeeding week. A minimum course consists of twelve weekly injections, although the course may be prolonged indefinitely. Prolonged use of the drug is usually productive of better results.

PRIMARY SYPHILITIC ATROPHY OF THE OPTIC NERVE

According to the statistical studies of Woods and Dunn [18] and Woods and Rowland,[19] primary atrophy of the optic nerve may be recognized not only as the most frequent neuropathy (71 per cent), but as most frequently due to syphilis (41 per cent). Igersheimer [20] has noted that 10 to 15 per cent of all patients with tabes dorsalis ultimately have atrophy of the optic nerve, which has been described [11] as "probably the most resistant feature of the most resistant form of neurosyphilis, i. e., tabes dorsalis." Usually unaccompanied by other syphilitic

15. Cornwall, L. H.; Bunker, H. A., and Myers, C. N.: Arsenic in the Spinal Fluid, Arch. Neurol. & Psychiat. **25**:137 (Jan.) 1931.

16. Moore, J. E.; Robinson, H. M., and Lyman, R. S.: Results of Tryparsamide Therapy in Syphilis, J. A. M. A. **83**:888 (Sept. 20) 1924.

17. (*a*) Moore, J. E.: The Modern Treatment of Syphilis, Springfield, Ill., Charles C Thomas, Publisher, 1941. (*b*) Stokes, J. H.: Modern Clinical Syphilology, Philadelphia, W. B. Saunders Company, 1934.

18. Dunn, J. R., and Woods, A. C.: Etiology Study of a Series of Optic Neuropathies, J. A. M. A. **80**:1113 (April 21) 1923.

19. Woods, A. C., and Rowland, W. M.: Etiologic Study of a Series of Optic Neuropathies, J. A. M. A. **97**:375 (Aug. 8) 1931.

20. Igersheimer, J.: Syphilis und Auge, Berlin, Julius Springer, 1918; Ueber der Opticusprozess bei Tabes und Paralyse, Deutsche med. Wchnschr. **52**:943, 1926.

disease of the eye, the process may be completed in several months or delayed by remissions over a period of several years. Optic nerve atrophy usually develops during the preataxic state, together with pupillary changes; the pallor of the disk appears first in the temporal portion but may quickly involve the entire nerve head. An extremely important observation with direct application to the problem of tryparsamide therapy was contributed by Traquair,[21] Dworjetz,[22] Somberg[23] and others, who noted that there is no relationship of either qualitative or quantitative character between the appearance of the nerve head and the functional capacity of the optic nerve. An appearance of atrophy may be associated with normal visual function, or, conversely, in developing atrophy, vision may be largely destroyed prior to ophthalmoscopic changes in the nerve head.

Stargardt[24] described the histopathologic changes of primary syphilitic optic nerve atrophy as glial proliferation in the nerve and the appearance of plasma cells in the contiguous pia; earliest involvement was noted in the chiasmatic region, and a similar process later appeared in the intracranial portion of the nerve, single or multiple areas being involved with dissimilar rates of progression. Once initiated the process consisted of progressive pial infiltration and glial proliferation; beneath infiltrated pial areas medullary sheaths showed marginal degenerative changes, which soon involved axis-cylinders, these being ultimately replaced by glial cells filled with amyloid. Intraneural connective tissue and blood vessels were not involved in the process even though far advanced atrophy was present. The relationship of the processes of inflammation and degeneration has remained obscure; apparently, as summarized by Moore,[25] the pathologic changes of primary atrophy are at first inflammatory and ultimately degenerative, the degenerative apparently being due to factors such as nutrition. Hauptmann[26] presented the assumption of a toxin mechanism of extracranial origin which produced degenerative changes through a selective action on the optic nerve; Wilbrand and Saenger[27] classified syphilitic involvement of the optic nerve as a simple perineuritis of the orbital and periorbital nerve. Neither of these explanations of the process is wholly tenable in view of the present understanding of the syphilitic process.

In the pia and arachnoid of the intracranial portion of the nerve, Igersheimer[20] has observed the presence of Spirochaeta pallida in equal numbers of cases of inflammatory changes of the nerve without degeneration and of optic nerve atrophy. On the other hand, production of optic nerve lesions by forms of S. pallida not yet microscopically identified (Saleeby and Greenbaum[28]) is worthy of deliberation.

That all atrophy of the optic nerve occurring when the serologic reactions are positive is not of the primary type was indicated by Igersheimer,[20] who enumerated additional ways in which atrophy may be produced by syphilis: in association with severe chorioretinitis of congenital syphilis; following the severe inflammatory reaction of acquired syphilis (in this instance the atrophy may be secondary);

21. Traquair, H. M.: Clinical Differentiation of Various Forms of Optic Atrophy, Brit. M. J. **2**:1157, 1922.

22. Dworjetz, M.: Atrophia Nervi Optici, Klin. Monatsbl. f. Augenh. **80**: 30, 1928.

23. Somberg, J. S.: Optic Nerve Pallor Without Functional Defects in Luetics, Am. J. Ophth. **10**:837, 1927.

24. Stargardt, K.: Ursachen des Sehnervenschwundes, Arch. f. Psychiat. **51**:711, 1913.

25. Moore, J. E.: Syphilitic Optic Atrophies, Medicine **11**:263, 1932.

26. Hauptmann, T.: Theorie auf Grund neuerer Forschungsergebnisse, Ztschr. f. d. ges Neurol. u. Psychiat. **128**:107, 1930.

27. Wilbrand, H., and Saenger, A.: Die Neurologie des Auges, Wiesbaden, J. F. Bergmann, 1913.

28. Saleeby, E., and Greenbaum, S.: Comparative Biologic and Histologic Study of Lymph Glands from Syphilis Patients, J. A. M. A. **96**:98 (Jan. 10) 1931.

accompanying gumma or periostitis of the orbit with pressure on the nerve; resulting from papillitis in basilar syphilitic meningitis, and following the pressure of syphilitic inflammatory products on the pathway from the orbit to the external geniculate bodies. By implication, then, atrophy of the optic nerve cannot always be designated as primary or secondary on the basis of ophthalmoscopic examination alone.

THE VISUAL FIELDS IN ATROPHY OF THE OPTIC NERVE

Moore [25] has suggested that field changes occur very likely as the initial clinical evidence of optic nerve atrophy and certainly before pallor of the optic disk is noted; such a suggestion, he pointed out, is a conjecture substantiated by frequent observation and by the comments of Igersheimer [20] who designated the first alteration of vision associated with syphilitic primary atrophy of the optic nerve as constriction of the visual fields for white and color, occurring prior to involvement of central vision. Either concentric (regular or irregular) contraction or sector-shaped defects were encountered, with the fields for color showing a type of defect similar to that of the field for form. Constriction of the fields for color occasionally preceded alteration of the field for form, with progressive loss first of green, then of red and finally of blue. Depression of green perception was held to imply involvement of the whole cross section of the nerve. Enlargement of the blindspot was described as an additional early symptom.

That there actually is a type of visual field characteristic of atrophy of the optic nerve was questioned by Uhthoff,[29] who designated two general types. In the first, perimetric reduction of the fields for form and color was associated with loss of both central and peripheral acuity; red-green perception was early involved, in contrast to blue-yellow perception, which was somewhat longer preserved. Such findings were presumed to be indicative of involvement of the entire cross section of the nerve. In the second type, abnormal portions of the visual field were sharply delimited from areas of normal function; sector defects and marked contractions of the field occurred. However, visual acuity and color sense were not implicated in the process, apparently because of a relative sparing of fibers serving the central portion of the retina. Circumferential syphilitic involvement of the optic nerve proper was assumed in the latter type of visual field. The possibility that sparing of the central portion of the retina was explained by the greater relative number of fibers supplying this region was suggested by Rönne,[30] who indicated that disproportionate loss of central and color vision might be best explained as loss of function of fibers subserving but a single function. Such disproportionate involvement, when occurring, was considered as an especially unfavorable indication of progression.

Uhthoff, quoted by Wilbrand and Saenger,[27] noted homonymous hemianopsia in 11 of 100 cases. This type of field is ascribed to syphilitic degeneration of vessels with secondary cerebral involvement, gummatous meningitis or syphilitic tumor of the optic tracts; Lissauer [31] and Marie [32] have noted it in dementia paralytica. Lillie [33] suggested that the appearance of homonymous hemianopsia in

29. Uhthoff, W.: Die Augenveränderungen bei den Erkrankungen des Nervensystems, in Graefe, A., and Saemisch, E. T.: Handbuch der gesamten Augenheilkunde, ed. 2, Leipzig, Wilhelm Engelmann, 1909.

30. Rönne, H.: Die Prognose der Sehnervenatrophie, Klin. Monatsbl. f. Augenh. **49**:154, 1911.

31. Lissauer, cited by Wilbrand and Saenger,[27] 1917, vol. 7.

32. Marie, cited by Wilbrand and Saenger,[27] 1917, vol. 7.

33. Lillie, W. I.: Tryparsamide Treatment of Syphilis of the Nervous System, J. A. M. A. **83**:809 (Sept. 13) 1924.

tabes dorsalis be regarded as due to "concurrent florid syphilis or to arteriosclerosis"; another type of defect, described by Lillie [34] as a "palpebral slitlike contraction," was described as being associated with syphilitic perineuritis of the optic nerve.

Arlt [35] classified the field defects of syphilitic patients as contraction for form and color, with reduction of central visual acuity, 85 per cent; sector-shaped defects, 9 per cent, and central scotoma, 6 per cent. With regard to central scotomas in syphilitic patients, von Hippel [27] has pointed out that they may frequently be more accurately ascribed to the amblyopia of alcohol, tobacco, sinus disease or diabetes than to tabes.

In classifying the field defects of 56 patients with a clinical diagnosis of primary syphilitic atrophy of the optic nerve, Sloan and Woods [36] designated concentric peripheral contraction in 7, a localized defect of the peripheral field in 19, central or cecocentral scotoma with normal peripheral fields in 8 and central or cecocentral scotoma with contracted fields in 22. In this series, central or cecocentral scotoma was present in over 50 per cent. Homonymous hemianopsia, previously referred to, was not noted as a visual field change associated with optic nerve atrophy and tabes dorsalis. This clinical study of 56 selected patients is the most complete investigation of its nature available in the literature; summarizing their material, Sloan and Woods [36] have been able to draw a remarkably close parallel between their clinical findings and the available pathologic data, already considered. It was noted that the primary lesion was certainly not behind the chiasm; further, bilateral symmetry of field defects was ascribed to multiple lesions of the optic nerve. They noted that if fibers supplying the peripheral portion of the retina have a peripheral location in the nerve, then various forms of field defects may be explained on the basis of a lesion starting in the periphery of the optic nerve. A diffuse lesion affecting the entire periphery of the nerve would produce concentric contraction of the field. Lesions of the foramen or of the intracranial portion of the nerve would be accompanied with late involvement of the cecocentral area of the field owing to the axial (central) location of the papillomacular bundle. If, however, a diffuse perineural lesion was located near the papilla, where this bundle is peripheral, it would produce a cecocentral scotoma in addition to peripheral contraction. Thus, isolated cecocentral scotomas, nasal steps and combinations of the two defects would result from a lesion in the anterior portion of the nerve which involved the papillomacular bundle, the fibers contiguous to it or both.

Their investigation further indicated that field defects for colored and for small white objects may either regress or completely disappear, a finding considered to be in accord with the conclusion of Stardgardt [24] that the primary lesion in syphilitic atrophy of the optic nerve is a peripheral and interstitial neuritis and that actual degeneration of the nerve fibers is secondary to this inflammatory change.

TRYPARSAMIDE THERAPY WHEN PRIMARY SYPHILITIC ATROPHY OF THE OPTIC NERVE EXISTS

If adequate therapy can be attained prior to the complete destruction of the nerve fibers, there is the possibility that the neuritic process may be controlled

34. Lillie, W. I.: Peculiar Contraction of Normal Visual Fields Associated with Syphilis of the Central Nervous System, Tr. Am. Ophth. Soc. **32**:153, 1934.

35. Arlt, E.: Behandelte und unbehandelte Fälle von tabischen Sehnerven Atrophie, Ztschr. f. ärztl Fortbild. **19**:367, 1922.

36. Sloan, L. L., and Woods, A. C.: Perimetric Studies in Syphilitic Optic Neuropathies, Arch. Ophth. **20**:201 (Aug.) 1938.

or prevented, according to Moore,[25] who has contended that antisyphilitic therapy in cases of primary syphilitic atrophy of the optic nerve offers hope only when instituted before visual loss has occurred. Such a comment lends emphasis to the necessity of early and accurate diagnosis of atrophy of the optic nerve. Disregarding the variable factors of remission and course, Moore has noted that not only has arsphenamine proved to be of little value in the treatment of optic nerve atrophy, but there is some indication that the course of degeneration may actually be accelerated; this comment is somewhat modified by the statement of Lillie,[33] who has ascribed renewed involvement of the optic nerve after the use of arsphenamine to a provocative reaction due possibly to inadequate doses of the drug. Lillie has recognized that damage to the optic nerve ascribed to tryparsamide may in many instances be a continuous degenerative syphilitic process. This view is based on the observation of 13 patients with visual disturbance (in 4 of these the disturbance was severe) among 114 patients receiving tryparsamide therapy. Examination of the visual fields of both tryparsamide-treated and untreated patients with optic nerve atrophy showed a similarity so marked that Lillie was able to conclude that visual damage was actually greater in the untreated patients than in the patients treated with tryparsamide and, further, that tryparsamide is no more harmful to the visual apparatus than either arsphenamine or sulfarsphenamine. (Parsons'[37] experience with sulfarsphenamine does not incline him to this view.) Neff[38] has summarized the results of treatment of 15 patients who had definite syphilitic ocular lesions prior to the use of tryparsamide; it is his conclusion that preexisting disease of this character does not adequately establish a contraindication to the use of tryparsamide.

In a study of 27 patients with all types of syphilitic ocular lesions prior to the use of tryparsamide, Cady and Alvis[39] noted the following results: 37 per cent became worse, 14.8 per cent improved and the lesions of 48.2 per cent did not change. Of the patients with optic nerve atrophy, treated with tryparsamide, as many progressed toward blindness as were not affected. The conclusions of these authors indicate that tryparsamide may be used with close observation if syphilitic disease of the optic nerve or syphilitic ocular disease is present. When mild deleterious effects from tryparsamide occur, discontinuance of treatment for one month was recommended, with resumption of treatment after the expiration of that interval.

A contrary view is presented by O'Leary[40] and by Moore, Robinson and Keidel,[41] who have concluded that syphilitic disease of the optic nerve does establish a contraindication to therapy with tryparsamide, a view apparently shared by Lorenz and associates.[43] Lees[44] treated 21 patients with established optic nerve

37. Parsons, R. P.: Tryparsamide and Sulpharsphenamine in Treatment of Neurosyphilis, U. S. Nav. M. Bull. **22**:526 (May) 1925.

38. Neff, E. E.: Effect of Tryparsamide on Optic Tract, Wisconsin M. J. **24**:120, 1925.

39. Cady, L. D., and Alvis, B. Y.: Use of Tryparsamide in Patients With and Without Ocular Lesions, J. A. M. A. **86**:184 (Jan. 16) 1926.

40. O'Leary, P. A.: Present-Day Status of Treatment of Neurosyphilis, J. A. M. A. **109**: 1163 (Oct. 9) 1937.

41. Moore, J. E.; Robinson, H. M., and Keidel, A.: Tryparsamide in Treatment of Syphilis, J. A. M. A. **82**:528 (Feb. 16) 1924.

42. Footnote deleted.

43. Lorenz, W. F.: The Treatment of Central Nervous System Syphilis with a New Arsenical, Wisconsin M. J. **20**:336, 1922. Lorenz, W. F.; Loevenhart, A. S.; Reitz, T. F., and Eck, C. P.: Use of Tryparsamide in Neurosyphilis, Am. J. M. Sc. **168**:157, 1924.

44. Lees, D.: Use of Tryparsamide in the Treatment of Syphilitic Optic Atrophy, Tr. Ophth. Soc. U. Kingdom **52**:203, 1932.

atrophy with tryparsamide and ascribed further deterioration of vision in 5 (severe and rapid in 2) to the direct action of the drug. Perhaps the most closely controlled series from the ophthalmologic standpoint was presented by Mayer and Smith,[45] who observed deleterious results in 3 of 14 patients with primary syphilitic atrophy of the optic nerve treated with tryparsamide; 2 of these patients recovered satisfactorily, but 1 case showed permanent contraction of the visual fields without impairment of central vision or alteration of the color of the nerve head. This series comprised 87 patients, and the authors concluded that "tryparsamide, intelligently administered, causes no increase in the atrophy of the optic discs, where syphilis has previously caused changes" and "causes no optic atrophy where the action of syphilis has not affected the discs."

The stringent ocular contraindications to the treatment of syphilis elaborated by Behr (quoted by von Hippel[46]) are, first, diminished central vision or loss of color vision with normal or near normal fields; second, concentric contraction of the fields both for form and for color with central vision normal; third, transitory visual field disturbance, especially in form, with normal central vision and optic nerve atrophy, and, fourth, subjective visual complaints. Von Hippel has commented that these restrictions exclude most patients with syphilis from therapy.

Woods and Moore[47] have indicated that preexisting syphilitic disease of the optic nerve or retina is not necessarily a contraindication to therapy with tryparsamide; this view is, however, modified by the comment that once evidence attributable to tryparsamide is present use of the drug should be discontinued. They have shown, also, that deleterious effects may be encountered in the use of tryparsamide in other diseases besides syphilis, namely, postencephalitic Parkinson syndrome, lymphosarcoma and trypanosomiasis.

In an extensive summary of the problem, Sutherland-Campbell[11] has indicated that there is basis for the view that both the syphilitic virus and tryparsamide have an affinity for the optic tract in certain cases; he stated the belief that the consensus indicates that toxic reactions to tryparsamide therapy occur rarely if the disks and fields are unaffected (by syphilitic disease) and, further, that an abnormality of either the fundi or the visual fields should preclude the use of tryparsamide. He recognized that many ophthalmologists contend that tryparsamide therapy should be employed in spite of changes in the eyegrounds or constriction of the fields. Mayer,[48] and Cordes in a discussion of Mayer's paper, supported this view. Sutherland-Campbell suggested that the finding of involvement of the optic nerve should contraindicate the use of tryparsamide therapy in general practice until more exact contraindications are available. Whatever measures are eventually adopted in the treatment of primary atrophy of the optic nerve, according to Sutherland-Campbell, tryparsamide "stands condemned" of dangerous potentialities in those cases of tabes dorsalis or dementia paralytica in which optic nerve atrophy is present.

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45. Mayer, L. L., and Smith, R. D.: Ocular Manifestations in Tryparsamide Treatment of Syphilis, Illinois M. J. **65**:258, 1934.

46. von Hippel, E., in Graefe, A., and Saemisch, E. T.: Handbuch der gesamten Augenheilkunde, Berlin, Julius Springer, 1923.

47. Woods, A. C., and Moore, J. E.: Visual Disturbances Produced by Tryparsamide, J. A. M. A. **82**:2105 (June 28) 1924.

48. Mayer, L. L.: Tryparsamide Therapy of Neurosyphilis and Atrophy of Optic Nerve. J. A. M. A. **109**:1793 (Nov. 27) 1937.

SUBJECTIVE OCULAR SYMPTOMS DURING TRYPARSAMIDE THERAPY

At the time that tryparsamide was introduced clinically, Lorenz and co-workers [3] stated that single doses as large as 5 Gm. were well tolerated except that transient amblyopia was occasionally produced. Their experimental work had indicated that the drug had an affinity for tissue of the nervous system; apparently for this reason these authors emphasized the fact that tryparsamide possesses the potentiality of injury to the optic tract and advised against administering it to patients showing degenerative changes of the optic nerve. Their later experience [43] with a 5 Gm. dose of tryparsamide weekly produced transient visual complaints in 40 per cent of their patients; on reduction of the dose to 3 Gm. the incidence of an unspecified type of visual disturbance was correspondingly reduced to 7 per cent. Brown and Pearce [2] noted occasional subjective complaints of dim vision twenty-four to seventy-two hours after the injection of tryparsamide; such symptoms were invariably temporary. Crawford [49] noted no complaints associated with the administration of the drug when small doses were given and was never obligated to discontinue administration for this reason. Downs and associates [50] in a closely observed (ophthalmologically) series of 223 patients who received 5,353 injections of 1 to 3 Gm. of tryparsamide noted reactions in 93, those in 44 per cent being subjective; among the patients with subjective symptoms, objective ocular findings were absent. In this series, 78 per cent of the patients noted the subjective effects (dim vision, sparks, distortion, flashes) prior to the tenth injection and 22 per cent after the tenth injection. In all but 1 of the latter group, comprising 9 patients, recurrence of subjective symptoms was noted during subsequent series of injections.

Woods and Moore [47] noted that 10.1 per cent of their patients receiving tryparsamide therapy made complaints of visual disturbance; in them, also, objective findings were absent. It was their observation that after subjective symptoms had disappeared even more intensive tryparsamide therapy could be administered without recurrence of a similar type of complaints and, further, the size of the dose apparently had relatively little to do with the production of this type of complaint; in fact, small doses were thought to produce more undesirable visual effects than did the larger doses. They recognized that patients with dementia paralytica or tabes dorsalis noted subjective disturbances more frequently than did patients with other types of neurosyphilis.

Moore and Sutton [51] have emphasized the importance of subjective symptoms in view of the fact that fundus changes and other objective findings are absent at the time subjective complaints are noted.

The administration of tryparsamide to patients who were not ophthalmologically retested despite the appearance of subjective complaints was described by Sloan and Woods.[52] One patient noted a subjective type of reaction after both the third and the eighteenth dose but retained normal vision although there was moderate contraction of the fields. The other patient noted subjective disturbance of vision after the third injection and progressed to blindness on the persistence of treatment. Both ultimately showed optic nerve atrophy, the former slight and the latter marked.

49. Crawford, E. M.: Tryparsamide Therapy in Neurosyphilis, Canad. M. A. J. **15**:46, 1925.

50. Downs, W. G.; McDermott, W., and Webster, B.: Reactions to Tryparsamide Therapy, Am. J. Syph., Gonor. & Ven. Dis. **25**:16, 1941.

51. Moore, J. R., and Sutton, I. C.: Tryparsamide in Treatment of Late Neurosyphilis, J. Nerv. & Ment. Dis. **63**:569, 1926.

52. Sloan, L. L., and Woods, A. C.: The Effect of Tryparsamide on the Eye, Am. J. Syph., Gonor. & Ven. Dis. **20**:583, 1936.

Among 52 patients (Ebaugh and Dickson [53]) and 100 patients (Solomon and Viets [54]) transient symptoms of unspecified character were noted; in both series, persistence of unfavorable effects was noted in a small percentage of patients treated.

In a review of the literature describing the treatment with tryparsamide of 2,087 patients without preexisting syphilitic lesions of the optic nerve, Sloan and Woods [52] noted an aggregate of 5.33 per cent of subjective reactions. These complaints consisted of dazzling, shimmering or tremor of vision, occurring transiently six to twenty-four hours after the injection; objective findings were absent.

Characteristic of the subjective reaction to tryparsamide therapy is the apparent intensification of the visual disturbance in positive illumination with diminution of symptoms in subdued illumination.[17]

OBJECTIVE IMPAIRMENT OF VISION DURING TRYPARSAMIDE THERAPY

Woods and Moore [47] observed that 5.5 per cent of their patients showed objective signs of visual damage during therapy with tryparsamide; final studies of this series after use of the drug was discontinued indicated that either complete recovery or severe permanent visual deterioration might result; avoidance of the latter permanent and severe sequela was accomplished by the withdrawal of the drug immediately on the appearance of symptoms. In this particular series of patients 94 per cent of the reactions appeared prior to the tenth injection of the drug and were considered by the investigators to be due to a direct toxic effect of the drug on the nerve or retina. The change in the visual field was described as contraction, involving especially the upper and lower nasal areas, with involvement of the temporal portion occurring infrequently. Among their patients showing unfavorable visual tolerance to the drug, 3 patients attained full recovery, 3 patients had a residuum of slight contraction of the fields (with normal vision), 5 patients had reduced central vision and 2 patients suffered severe permanent damage.

Downs and associates,[50] previously referred to, noted that 52 patients among 223 receiving tryparsamide had objective reactions; of these, 20 patients had reactions described as mild, consisting of moderate contraction of the fields, especially in the nasal portion, together with depression of the visual acuity. The changes disappeared when use of the drug was discontinued. The reactions in 11 patients appeared prior to the tenth injection and those in 9 after the tenth injection. An additional 27 patients had reactions designated as moderately severe, characterized by contraction of the fields and depression of central vision, neither of which type of change was permanent. In this group, the reactions in 17 patients occurred prior to the tenth injection and those in 10 occurred later.

Pearce [55] discussed the use of tryparsamide in 77 patients with trypanosomiasis; objective reactions occurred in 9 but permanent damage was detected in only 3 of these patients. Powell and Smith [56] described constriction of the fields in 11 of 16 patients during routine administration of tryparsamide. Three patients showed no change, and 5 showed an initial expansion followed by subsequent contraction. Moderate contraction following an initial expansion possibly due to the tonic

53. Ebaugh, F. G., and Dickson, R. W.: Tryparsamide in the Treatment of General Paralysis, J. A. M. A. **83**:803 (Sept. 13) 1924.

54. Solomon, H. C., and Viets, H. R.: A Comparison of Tryparsamide and Other Drugs in Treatment of Neurosyphilis, J. A. M. A. **83**:891 (Sept. 20) 1924.

55. Pearce, L.: Studies on Treatment of Human Trypanosomiasis with Tryparsamide, J. Exper. Med. **34**:1, 1921.

56. Powell, L. S., and Smith, H. S.: Studies of Visual Fields in Connection with Tryparsamide Therapy, Arch. Ophth. **24**:276 (Aug.) 1940.

effect of the drug was considered as a usual occurrence rather than as a reaction to the drug, which did not occur in this series. Among 4 patients with objective reactions among 85 syphilitic patients receiving tryparsamide, Wile and Wieder [57] noted that in 1, in addition to blurring of the vision, a neuroretinitis with contraction of the fields for form and color developed.

Cady and Alvis [39] have noted that statistical studies of poor results are frequently associated with limited numbers of patients, and they have attributed unfavorable visual effects to inadequate experience with the drug. In their closely studied (ophthalmologically) series of patients free of detectable syphilis-produced ocular lesions, only 5.2 per cent manifested involvement due to tryparsamide. Permanent change, however, occurred in only 1.3 per cent of persons who prior to use of tryparsamide were free of optic neuritis, optic nerve atrophy or syphilis-produced change in vision, fundi or visual fields.

Sloan and Woods [52] noted in their summary (previously referred to) of 2,087 reports in the literature on patients in whom prior syphilitic involvement of the optic nerve was not apparent that 3.53 per cent of the patients presented objective evidence of damage due to tryparsamide. In the reaction which they classified as "chronic," changes are noted primarily in the visual fields, with central vision relatively undisturbed. The upper and lower portions of the fields nasally were involved. Scotomas were not present, nor was either the blindspot or the color vision altered. Constriction of the fields, once developed, tended to be permanent; visual loss usually stopped short of blindness if use of the drug was discontinued.

Sloan and Woods [52] indicated that the peripheral field defects of tryparsamide therapy and of syphilitic atrophy of the optic nerve are similar in that there is greater contraction proportionally for white than for blue or red and a greater defect for red than for blue, the latter finding being common to all early lesions of the conduction path. Field defects of syphilitic atrophy of the optic nerve do not show relative sparing of the temporal field and contraction of the upper and lower nasal fields, as is consistently the case with tryparsamide. In damage due to tryparsamide the far periphery of the field is affected most severely, the midperiphery only slightly and the central field not at all, except in very severe reactions, this fact indicating a lesion which does not affect the entire cross section of the nerve at the same time. They did not agree with Lillie in his view that the visual field defects accompanying tryparsamide therapy are due to reactivation of a latent syphilitic optic nerve atrophy and suggested that if a direct neuritic involvement of the peripheral nerve occurs the lesion cannot be near the bulb, where the papillomacular bundle, not usually involved, is located. Infrequence of pallor of the disk supports such a view. Further, if reactivation of the syphilitic process were the explanation of visual involvement, then sparing of the temporal field would not be possible.

Lillie [33] has indicated that the impression of a direct toxic effect due to tryparsamide may be questioned, as such an occurrence should produce loss of central vision due to central scotomas. His understanding of this relationship of tryparsamide to syphilitic disease of the eye has been considered.

Stokes and Wilhelm [58] noted 8 patients with objective visual reactions among 152 patients and emphasized that normal vision and fundi are compatible with marked constriction of the visual fields. These patients, together with others on

57. Wile, U. J., and Wieder, L. M.: Tryparsamide in the Treatment of Neurosyphilis, J. A. M. A. **84**:1710 (June 6) 1925.

58. Stokes, J. H., and Wilhelm, L. F. X.: Tryparsamide in the Treatment of Neurosyphilis, Arch. Dermat. & Syph. **11**:579 (May) 1925.

whom detailed ocular studies were made, were the basis of a report by O'Leary and Becker,[59] in which subjective reactions were noted in 14 patients and objective reactions in 9. Among the latter, 5 patients retained permanent damage; in 3 this was contraction of the fields and in 2 homonymous hemianopsia. The reports of Kirby and Hinsie,[60] Campbell,[61] Gibbs and Reichenbach,[62] Berg,[63] Neymann and Singleton,[64] Silverston,[65] Kibler,[66] Branche,[67] Lazar [68] and Cormia [69] may be summarized as follows: 413 cases were presented, with the occurrence of objective reactions in 19. In general, the cases were inadequately studied ophthalmologically for statistical purposes. Subjective complaints were not described by the various authors. It is noted that there was an aggregate of 4.5 per cent of objective reactions.

Mayer and Smith [45] presented a series of 72 patients in whom no indication of syphilitic involvement of the eye was noted; extremely careful ophthalmologic examinations were made at repeated intervals, which included colorimetric estimation of the disk. They were able to detect objective reactions in 5; none had residual loss of vision on follow-up examination.

ALTERATION OF LIGHT SENSE DURING TRYPARSAMIDE THERAPY

In association with objective ocular changes Sloan and Woods [52] have described the light sense as altered by tryparsamide therapy. It was their preliminary impression, based on the study of 8 patients who received tryparsamide as compared with 77 patients with syphilis of the central nervous system without ocular involvement who did not receive tryparsamide, that a reduction in sensitivity to light occurred in every patient with contraction of the fields or pallor of the disk which followed the use of tryparsamide, and, further, a quantitative evaluation of the severity of the tryparsamide reaction in a few patients seemed to be possible. However, a normal curve for certain patients with marked field contraction following tryparsamide therapy suggested that the test is of less value in detecting objective damage than is perimetry. Peripheral meridional measurements, however, were anticipated to show depression of the light sense at the onset of untoward effects of tryparsamide.

ACUTE VISUAL REACTION TO TRYPARSAMIDE THERAPY

Five patients among 223 treated and reported on by Downs and associates [50] experienced sudden complete loss of central and peripheral vision. The ultimate

59. O'Leary, P. A., and Becker, S. W.: Further Observations on the Treatment of Neurosyphilis with Tryparsamide, M. J. & Rec. **123**:305, 1926.

60. Kirby, G. H., and Hinsie, L. E.: Tryparsamide Treatment of General Paralysis, State Hosp. Quart. **12**:53, 1926.

61. Campbell, G. B.: Treatment of General Paralysis by the Use of Tryparsamide, State Hosp. Quart. **12**:76, 1926.

62. Gibbs, C. E., and Reichenbach, E. B.: Tryparsamide in General Paralysis, State Hosp. Quart. **12**:82, 1926.

63. Berg, L.: Results with Tryparsamide in the Treatment of Neurosyphilis, Am. J. Syph. **10**:261, 1926.

64. Neymann, C. A., and Singleton, D. E.: Therapeutic Results with Tryparsamide in the Treatment of Neurosyphilis, J. Nerv. & Ment. Dis. **64**:144, 1926.

65. Silverston, J. D.: Observations on Tryparsamide Therapy in Neurosyphilis, Lancet **2**:693, 1926.

66. Kibler, O.: The Value of Intensive Treatment with Tryparsamide and Mercury in General Paralysis, Illinois M. J. **59**:117, 1931.

67. Branche, G. C.: Tryparsamide Therapy of Neurosyphilis in Negroes, U. S. Vet. Bur. M. Bull. **7**:476, 1931.

68. Lazar, N. K.: Effect of Tryparsamide on the Eye, Arch. Ophth. **11**:240 (Feb.) 1934.

69. Cormia, F. E.: Tryparsamide in Treatment of Syphilis of the Nervous System, Brit. J. Ven. Dis. **10**:99, 1934.

result was permanent contraction of the field and diminished visual acuity. Four of these severe reactions occurred prior to the tenth injection; one occurred after the tenth injection.

King [70] reported in detail the course of 1 patient with a severe reaction to tryparsamide. There had been no preliminary ocular examination; reduced vision was noted ten days after the third injection, associated with contraction of the fields for white and color and central scotoma in each eye. There was pallor of the disks. In two weeks the vision improved, with disappearance of the central scotoma, but the visual fields remained contracted. The peripheral fields showed progressive contraction, with complete blindness ensuing five months later. Smith [71] noted 2 patients with acute reactions among 45 patients treated with tryparsamide. One of these showed complete recovery in five weeks; the other (with indications of preceding syphilitic damage) showed approximately 50 per cent recovery.

Casten [72] has described an acute reaction occurring in normal eyes subsequent to the second injection. With forced drainage of the cerebrospinal fluid as immediate treatment, and repetition of the procedure on four occasions, gradual improvement of vision to 20/15 with an expansion of the fields to near normal was noted in four months. Sloan and Woods [36] have reported a similar reaction occurring after the administration of 3 Gm. of tryparsamide; treatment with typhoid vaccine, malaria inoculations and forced drainage of the cerebrospinal fluid was accomplished, with the return of vision from perception of shadow to 20/20 and only moderate depression of the visual fields seven months after visual impairment occurred.

Fine,[73] Weeks,[74] Woods and Moore [47] and Sharpe [75] have described briefly and without great detail acute reactions to tryparsamide therapy.

Muncy [76] has advocated the use of vitamin B concentrate in the treatment of acute reactions to tryparsamide; Leinfelder [77] has not been able to duplicate the reported satisfactory results of return of visual function.

MECHANISM OF TRYPARSAMIDE DAMAGE TO NERVE AND RETINA

Young and Loevenhart,[78] in studying the experimental toxicity of various arsenicals with reference to the ocular system, noted that arsenicals with the amino group, or substituted amino group, in the para position to the arsenic produced lesions in the rabbit retina. It was their observation that if the amino group, or its substitute group, were in the ortho or meta position to arsenic no lesion was produced in the optic nerve. Thus, it was suggested that the position of the amino group, or its substitute, was of greater significance with relation to the production

70. King, O. H.: Eye Contraindications to Arsenical Treatment of Syphilis, South. M. J. **20**:284, 1927.

71. Smith, E. R.: Tryparsamide in Neurosyphilis, J. Indiana M. A. **18**:125, 1925.

72. Casten, V.: Tryparsamide Amblyopia Treated by Forced Drainage of Cerebrospinal Fluid, New England J. Med. **202**:676, 1930.

73. Fine, M., in discussion on Leinfelder.[80]

74. Weeks, J. E., in discussion on Leinfelder.[80]

75. Sharpe, O. A., in discussion on Leinfelder.[80]

76. Muncy, W. M.: Relationship of Tryparsamide Reaction to Vitamin Deficiency, Tr. Am. Acad. Ophth. **44**:134, 1939.

77. Leinfelder, P. J., and Stump, R. B.: Thiamine Hydrochloride in Treatment of Tryparsamide Amblyopia, Arch. Ophth. **26**:613 (Oct.) 1941.

78. Young, A. G., and Loevenhart, A. S.: Relation of Chemical Constitution of Certain Organic Arsenical Compounds to Their Action on the Optic Tract, J. Pharmacol. & Exper. Therap. **23**:107, 1924.

of ocular damage than was the valence of the arsenic. The dose of tryparsamide used in their experiments was comparatively larger than that used clinically.

The possibility of systemic retention of tryparsamide after injection, with cumulative toxic action, is in part answered by the studies of Young and Muehlberger [79]; 3 of 4 patients observed excreted 88 to 95 per cent of the drug unchanged in the urine during the first twenty-four hours after injection. It was concluded that certain persons may show a slower excretion rate, this possibly increasing the likelihood of ocular reaction. Leinfelder [80] has commented that disintegration of pentavalent arsenicals which remain in the blood stream is very slow. Osborne [81] has experimentally shown that arsenic can be identified in the brain of rabbits after therapeutic doses of tryparsamide, but Leinfelder has noted that neither arsenic nor the aniline group will cause the tryparsamide type of field defect characterized by peripheral contraction. Whether or not arsenic derived from tryparsamide reaches the cerebrospinal fluid has been considered.

A histopathologic study of the retina and optic nerves and tracts has been presented by Leinfelder.[80] After an intravenous dose of 1 Gm. of tryparsamide vision decreased from normal to amblyopia in each eye; death occurred from uremia nine days later. Prior to death a moderate degree of optic nerve atrophy had been noted; this was represented in the postmortem specimens as a slight gliosis without inflammatory or acute degenerative change. The nerve sheaths were normal. In the retina gliosis of the nerve head was correlated with the preexisting optic nerve atrophy. In the central portion of the retina areas of degenerative change were noted in the inner nuclear layer; cellular and nuclear structure could not be delineated. In the peripheral portion of the retina, where the greatest change was noted, ganglion cells had a cloudy or foamy cytoplasmic appearance; Nissl substance had largely disappeared, and nuclei were mostly destroyed. The nuclear degeneration and loss of Nissl substance were compared by Leinfelder to the marked cellular reaction occurring in acute intoxications of the central nervous system. A corresponding acute degenerative process was not noted in the optic nerves or tracts or in the lateral geniculate bodies; it was considered that the primary occurrence was a degeneration of the ganglion cells of the retina with secondary degeneration of both nerve fibers and myelin sheaths. With reference to this case, Leinfelder was able to comment that at least the factors of arteriosclerosis and alcoholism were not present and to conclude that ocular reactions following tryparsamide therapy are most likely of the nature of idiosyncrasy to the drug, a view supported by Cordes in a discussion of Leinfelder's case and by Woods and Moore.[47]

In a similar study, Lazar [68] concluded that the histopathologic changes of a patient blinded three years before death by tryparsamide were those of syphilis rather than the result of the use of tryparsamide.

Sézary and de Font-Réaulx [82] stated the belief that ocular damage is due to toxic action of the drug on the optic nerve rather than to reactivation of a latent lesion of the disease itself, a view which they stated was substantiated by studies which show degeneration rather than inflammation; their observation on patients

79. Young, A. G., and Muehlberger, C. W.: Excretion of Tryparsamide, J. Pharmacol. & Exper. Therap. **23**:461, 1924.

80. Leinfelder, P. J.: Pathologic Changes in Amblyopia Following Tryparsamide Therapy, J. A. M. A. **111**:1276 (Oct. 1) 1938.

81. Osborne, E. D.; Putnam, E. D., and Hitchcock, B. S: Effect of Arsenic on Rabbits, Arch. Dermat. & Syph. **25**:419 (March) 1932.

82. Sézary, A., and de Font-Réaulx, P.: La névrite optique de l'arsenic pentavalent, Ann. de dermat. et syph. **4**:289, 1933; cited by Sloan and Woods.[52]

with optic nerve atrophy treated with sodium arsanilate and tryparsamide who had neither syphilis nor trypanosomiasis, and finally, the experimental evidence that these ocular changes can be reproduced in animals by giving them pentavalent arsenicals. The fact that ocular complications occur with greater frequency in patients with involvement of the nervous system and may occur after only a few injections has been advanced as an argument in favor of reactivation of the lesion. Sézary and de Font-Réaulx suggested that a preexisting lesion may render nerve fibers more liable to injury by the toxic action of the pentavalent drug.

Apparent activation of a syphilitic process by tryparsamide with deleterious effects on the optic nerve was described by Lillie [33] when he reported a case of tabes dorsalis in which the vision and visual fields were normal prior to antisyphilitic therapy. Arsphenamine, sulfarsphenamine and tryparsamide were administered. A contraction of the fields described as slitlike occurred; this apparently was not related to any specific drug. Diffuse degeneration of the nerves, more pronounced in the periphery, was noted at necropsy, at which time a pathologic diagnosis of perineuritis was made.

LEGAL ASPECTS OF TRYPARSAMIDE THERAPY

The important legal aspects of the uncontrolled (ophthalmologically) administration of tryparsamide associated with detrimental visual sequelae are well exemplified by the following court action (Reed versus Church [83]). During a period of fourteen years following initial treatment of cerebrospinal syphilis in 1923 a plaintiff enjoyed good health. His eyesight was good although a pair of glasses was purchased in 1930. In 1937 this plaintiff fainted suddenly and on reexamination was noted to have violent headache and incoherence of speech. The defendant physician certified at this time that the patient was suffering from severe hypertension. Despite this diagnosis and a negative Wassermann reaction of the blood, the defendant physician concluded that the plaintiff had a recurrence of cerebrospinal syphilis and commenced to administer a series of injections of tryparsamide. This drug, an arsenic compound, was sold in ampules around each of which was a pamphlet advising, among other things, that treatment be discontinued immediately on the appearance of any ocular disturbance. After, or at the time of, the third injection the plaintiff complained that the injections were making his eyes a little blurry, but each time he complained the defendant physician advised him that his difficulty would clear up. It did not, however, and the plaintiff subsequently became almost completely blind, with "central," or "gun barrel," vision due to permanent optic nerve atrophy. The plaintiff brought suit against the defendant physician for malpractice and obtained a judgment in his favor. The defendant physician then appealed to the Supreme Court of Appeals of Virginia. The plaintiff testified that after he had complained of having trouble with his eyes the defendant continued the tryparsamide treatment and gave him in all nine injections. The defendant maintained that there were two schools of medical opinion as to whether the use of tryparsamide should be continued after the discovery of ocular disturbances. The one theory reasoned that the continued use of the drug by helping the syphilis would help the optical disturbances; the other theory suggested that use of the drug be discontinued immediately on the complaint of visual trouble. The defendant therefore contended that if he followed either one of these theories

83. Malpractice—Liability of Physician for Blindness Caused by Administration of Tryparsamide [Reed vs. Church], Medicolegal Abstract, report of the Bureau of Legal Medicine and Legislation, J. A. M. A. **116**:891 (March 1) 1941.

he had not been negligent. The court held that the defendant's testimony "that he stopped giving the injections after the plaintiff complained about his vision" committed him to the second school of medical opinion. However, since his testimony in that regard was disputed by the plaintiff, it was the opinion of the court that the important question for the jury's determination did not relate to the rule that when there are two schools of thought in medical practice if the physician follows one he cannot be negligent, but did relate to whether or not the defendant properly and carefully followed the branch of medical opinion which he had adopted. On this point the jury resolved the question against him. A physician, continued the court, is liable only for a failure to possess and exercise that degree of care and skill ordinarily exercised by prudent practitioners in his community. In the present case, therefore, the plaintiff was required to show that his blindness was caused not by the cerebrospinal syphilis but by the injections of tryparsamide and that those injections were given in contravention of good practice in that community. If it were equally probable that the blindness was caused by either, the plaintiff could not recover. Evidence showed that it is well known in medical circles that either the cerebrospinal syphilis or the injections of tryparsamide could cause serious ocular trouble. Two physicians did testify that in their opinion the atrophy of the plaintiff's optic nerve was of syphilitic origin, but they admitted that it was impossible to determine by examination whether this was due to syphilis or to arsenical poisoning. It would appear that no amount of clinical research could determine which of the forces here at work caused the atrophy; so it was for the jury to waive the probability and decide. The jury did so and found, which finding in the opinion of the court was justified by the evidence, that it was not equally probable that syphilis caused the ocular trouble, but rather that the defendant's treatment was the proximate cause of optic nerve atrophy. The evidence showed that for fourteen years after being treated for syphilis the plaintiff had had no ocular trouble; that in 1937, despite a negative Wassermann reaction, the defendant treated him for syphilis with tryparsamide, a potent drug which should be administered only under ocular control, which the defendant failed to exercise; that in spite of the plaintiff's complaint of increasing visual disturbances the defendant continued the injections of the drug, and that more than a year later the plaintiff underwent an extensive examination for the presence of syphilis which proved to give negative results, although the blindness remained. Because there was evidence, though conflicting, that at the time the plaintiff fainted on Aug. 14, 1937 he had a headache, an elevation of blood pressure and incoherence of speech, and in view of his age of almost 62 years, the oppressive heat at the time and the negative Wassermann reaction, the court was of the opinion that there was evidence from which the jury might have concluded that there was not sufficient proof of the recurrence of syphilis to justify the defendant in administering tryparsamide in an uncontrolled manner. In fact, there was medical testimony that such treatment, persistently administered despite increasing loss of vision, may be proper only in the case of an extremely aggravated syphilitic condition, and there was evidence that in the present case no such condition existed. The court, therefore, refused to disturb the jury's verdict and affirmed the judgment for the plaintiff.

SUMMARY

It is manifest according to material accessible to review that a precise evaluation of the various factors that contribute to impairment of vision during therapy with tryparsamide is not to be derived from the literature on the subject. In the introduction to this review the factors operating to veil the entire subject in factual

obscurity were elucidated. Such analytic data as may be reasonably derived are approximately as follows:

There is noted no indication that sex, race or age of the patient is related to untoward visual effect during therapy with tryparsamide. This generalization must allow, however, for two possible discrepancies. Neurosyphilis usually and tabes dorsalis certainly are disease processes of the middle decades of life; the use of tryparsamide exclusively for these conditions suggests that factual data based on investigational material for other age groups would not be available and that statistics regarding this subject would not be applicable to the earlier or later decades of life. It has been noted that reports pertinent to the visual effects of tryparsamide therapy appearing in the foreign literature have shown both a higher and a lower incidence of unfavorable visual involvement than has been noted in the recent domestic literature. The fact that tryparsamide was first available in this country would suggest that the recent discrepancies of the foreign literature are comparable to the confusion indicated in American literature during the first years after the clinical introduction of the drug into this country. With reference to sex and race, no data of considered significance were obtained.

The dose of the individual injection, the number of injections and the length and number of courses of injections have not been noted to be associated with visual effects in a consistent manner. On one occasion the comment was made that "smaller doses tended to be more productive of unfavorable (visual) results." In the absence of verification of this observation, it is not possible to offer the conclusion that the amount of the individual dose explains the visual reaction. The number of doses of tryparsamide has long been a factor acknowledged to be associated with visual deterioration. It is generally considered that if untoward effects are to occur, these will be noted prior to the tenth injection. Evidence of such a belief is current throughout the literature. Statistically, however, such a presupposition is apparently poorly borne out, and in the light of the figures presented, which are the most complete available on this particular phase of the subject (Downs [50]), the opinion is best modified to state that most reactions, especially "acute" ones, are noted relatively early in the series of tryparsamide injections, but such a statement must not preclude recognition that deleterious effects may occur later in the period of treatment.

With regard to the character of the reaction which occurs during a series of tryparsamide injections the classification of Sloan and Woods is of assistance. Types of visual effects are designated by them as acute and chronic, with the latter type subdivided into objective and subjective. The chronic subjective reaction is characterized as occurring in approximately 5 to 10 per cent of patients receiving tryparsamide therapy and consists of flashes, sparks or spots before the eyes, together with visual distortions and slightly decreased central visual acuity. Objective findings are not usually detected; the prognosis is good if therapy is discontinued.

With regard to the subjective type of reaction, patients frequently have visual complaints based primarily on their apprehension; many patients are prone to answer in the affirmative regarding visual phenomena, and close interrogation with regard to the exact character of such occurrences is desirable before a decision to discontinue use of the drug is made.

Objective chronic reactions are specified to occur in a smaller number of patients (4 to 5 per cent) receiving tryparsamide therapy, with permanent unfavorable results in about 1 per cent. This type of reaction consists of contraction of the visual field, involving primarily the upper and lower nasal areas, with relative

sparing of the temporal portions. Moderate depression of central vision is frequently noted; central scotomas and enlargement of the blindspot are not characteristic of this type of reaction. The prognosis regarding restoration of vision is held to be good if the condition is recognized and the drug withdrawn promptly. There is sufficient evidence that after an initial visual reaction the deleterious effect will recur on resumption of tryparsamide therapy to render it advisable to withdraw the drug permanently once an untoward effect of either an objective or a subjective character is noted.

During routine administration an initial expansion of the fields with later moderate contraction of the peripheral field has been described as a usual occurrence. It is possibly incorrect to refer to such minimal contraction as a reaction, although it is reasonably inferred that such an occurrence must, nevertheless, be of the nature of a reaction.

Acute reactions are distinct from chronic reactions in all characteristics, including, possibly, even causation. The percentage incidence of such reactions to tryparsamide therapy is not disclosed in a review of the literature; certainly, however, they are much more infrequent than chronic ones. Usually occurring prior to the fifth injection of the drug, they are characterized by rapid deterioration of both central and peripheral vision. Complete details in a sufficient number of cases are not available in the literature to indicate in a satisfactory manner the actual outcome of the original visual deterioration. Such cases as are deemed eligible in a statistical consideration of the prognosis of such reactions indicate that in approximately one half permanent visual loss will obtain, while in the other half relatively complete restoration of vision may occur.

The foremost question with regard to the use of tryparsamide has revolved around the question of atrophy of the optic nerve and the suspected effect of the drug when this condition is noted prior to the initiation of tryparsamide therapy. It is permissible to state that opinion in regard to this matter as reflected in the literature is approximately equally divided among physicians who when primary syphilitic optic nerve atrophy is present would withhold the drug and those who under similar conditions would favor its use. Any preponderance of opinion evaluated in terms of the evidence presented would incline to the view that detectable syphilitic involvement of the visual tracts offers some type of predisposition or possibly sensitization to the drug, but there is lacking indication that the presence of optic nerve atrophy actually establishes a satisfactory contraindication to use of the drug. When optic nerve atrophy is present possible arbitration of the problem is best accomplished by closer surveillance of the patient before and during tryparsamide therapy than would otherwise be offered, with immediate and permanent withdrawal of the drug if tangible evidence is obtained that the drug is actually contributing to the further deterioration of vision. The consensus is complete that remissions of the process of primary syphilitic optic nerve atrophy, together with recurrences of the process, are common to tabes dorsalis, and such conditions must not be confused with a suspected effect of tryparsamide therapy. In view of the hopeless course of primary syphilitic optic nerve atrophy when untreated, and the fact that other treatment (with the exception of fever therapy), offers little or no hope of arresting the process, and in recognition also that beneficial action may be received from the use of tryparsamide to the same extent that deleterious effects may occur, it seems inadvisable to permit the establishment of any rule as such to govern therapy with tryparsamide or withholding of the drug.

That the differential diagnosis between the normal condition of the optic disk and that of primary syphilitic optic nerve atrophy is not always clearcut is attested by the fact that the color of the disk, the visual acuity and the visual field findings may yield contradictory evidence. With the introduction of the numerous complex factors associated with visual impairment during treatment with tryparsamide, confusion as to the probable cause of visual impairment is present. Of the various examinations available, apparently the examination of the visual fields offers the most thorough information in regard to the exact nature of impairment of vision. The visual field defects of optic nerve atrophy are described as concentric peripheral contraction, localized defects in the peripheral fields and central or cecocentral scotomas. The peripheral contraction is moderate and affects especially the nasal portion, usually with sparing of central vision.

The intimate or exact nature of the reaction to tryparsamide remains obscure in the literature. Repeatedly suggested to explain visual involvement are a hypothetic toxic effect of the drug on the nerve or retina, idiosyncrasy to the drug, factors superimposed by drug therapy on active syphilitic involvement (reactivation of a process) and the Jarisch-Herxheimer reaction. Factors such as the valence of the arsenic in the preparation, the structure of the tryparsamide molecule and the factors of retention-excretion and metabolism have been considered without the establishment of a conclusive opinion concerning the mechanisms of the reaction.

The relatively infrequent occurrence of systemic effects is against any theory holding tryparsamide to be a toxic drug generally; contrarily, the type of visual impairment is suggestive of a toxic effect in the nature of an idiosyncrasy, especially in the acute reactions. There is an absence of proof that syphilis or any other condition predisposes to a reaction to tryparsamide. There is, however, the implication that the exact mechanism of the acute and of the chronic type of reaction may be different. In the light of the clinical and pathologic material available in the literature, other factors functioning to produce visual involvement cannot be adequately evaluated. There is no indication that the use of the drug should be condemned; contrarily, therapy is fully desirable, but closer observation ophthalmologically of patients, certainly during the preliminary stages of therapy, seems the most desirable conclusion of the clinical aspects of the problem.

816 Strand.

News and Notes

EDITED BY DR. W. L. BENEDICT

SPECIAL NEWS

A dinner in honor of Dr. Walter B. Lancaster was given on October 14 at the Coronado Hotel, St. Louis, by the St. Louis Society for the Blind, in cooperation with the National Society for the Prevention of Blindness and the Association for Research in Ophthalmology. The dinner was given on the occasion of the award of the Leslie Dana Medal for the Prevention of Blindness.

SOCIETY NEWS

Canadian Ophthalmological Society.—The sixth annual meeting of the Canadian Ophthalmological Society was held at Toronto, Canada, Sept. 24 and 25, 1943.

The following papers were presented:

"Color Photography of External Disease," A. Lloyd Morgan, M.D., Toronto; "Corneal-Scleral Suture," R. J. P. McCulloch, M.D., Toronto; "Sulfonamide Compounds in Local Ocular Conditions," Alson E. Braley, M.D. (by invitation), New York; "Mixed Cell Tumors of the Lacrimal Glands," J. A. MacMillan, M.D., Montreal; "Ophthalmologic Research in the Royal Canadian Navy," Surgeon Commander C. H. Best and Surgeon Lieutenant Commander Donald Y. Solandt, Toronto; "Orthoptics in Aviation," Squadron Leader J. V. V. Nicholls, M.D., Montreal; "Orbital Implants," W. W. Wright, M.D., Toronto; "Ariboflavinosis and Circumcorneal Congestion in the Navy," Surgeon Commander E. A. Amos, R.C.N.V.R.; "Retinal Arterial Tension in Epilepsy," G. A. Stuart Ramsay, M.D., Montreal; "Hereditary Disease of the Eye," Madge T. Macklin, M.D., London, Ontario; "Amaurosis Caused by Blastocytoma of Adrenal," Colin Campbell, M.D., Toronto; "Colored Moving Pictures of Eye Operations," Major J. P. Gilhooly, R.C.A.M.C., Ottawa, Ontario.

Asociación para evitar la ceguera en Mexico.—Dr. William Thornwall Davis was invited to read a paper on Aug. 17, 1943 before the Asociación para evitar la ceguera en Mexico (Society for the Prevention of Blindness in Mexico) on amblyopia ex anopsia. Since he was unable to deliver the paper personally, the department of ophthalmology of the George Washington University School of Medicine made a sound film of the paper in Spanish, which was sent by mail to Mexico and produced at the meeting of the association on the date appointed. Dr. Davis read the introductory paragraphs of the paper, and Dr. Castillo Najera, of the George Washington University School of Medicine, 1942, read the main body of the paper for Dr. Davis.

UNIVERSITY NEWS

Ophthalmologic Research at the University of Oxford.—An announcement in *Science* (**98:** 318 [Oct. 8] 1943) states:

"The University of Oxford is planning the establishment of a department for ophthalmological research, the activities of which would include research, teaching and the treatment of patients. The Ophthalmological Research Endowment Committee is asking for help in raising £250,000 to build, equip and endow the research laboratories of a department of ophthalmology at the university. Contributions received during the war will be invested in Government securities. The treasurer of the Ophthalmological Research Endowment Fund, Old Clarendon Building,

Oxford, will receive contributions. Expenses of the appeal are being met by the generosity of the National Institute for the Blind. *The Times,* London, reports that

"'The facilities available for such work are considered wholly inadequate, and the university is appealing for funds towards the establishment of research premises in connection with the Oxford Eye Hospital, the rebuilding of which will be begun at the end of the war; the provision of salaries for full-time and part-time research workers, teachers and technicians engaged in the new department; and the defraying of the working costs of researches which would have for their aim the prevention of blindness, the improved treatment of eye disease and the promotion of a higher standard of visual function throughout the country.

"'Under the proposed regional scheme of the Joint Hospitals Board, the Oxford Eye Hospital will become the chief regional center (covering the counties of Oxford, Buckingham and Berkshire) for ophthalmological work and teaching. For this the present hospital is inadequate, and is to be rebuilt, the necessary funds being raised by a separate appeal from local sources.

"'One of the problems which the proposed department at Oxford would examine would be that of discovering the safest anti-bacterial drugs for ophthalmological purposes. The extreme delicacy of the eye is the governing consideration, as all the usual antiseptics are poisons, and further investigation will need contributions not only from ophthalmology, but bacteriology, mycology and chemistry. The most promising substance found so far is penicillin, the development of which is largely the result of work done in an Oxford laboratory.

"'The Oxford scheme, which will be generally welcomed, will form an important contribution towards the great national effort that is being made to abate the toll and suffering and economic wastage due to loss of sight and defective vision. Statistics prove that, while failure of vision is a hazard common to all, the risk falls increasingly on those who are in middle and later life. In 1941 out of a total blind population of 74,000 in England and Wales, 63,000 were persons over 40 years old.'"

Obituaries

GEORGE HUSTON BELL, M.D.
1866–1943

Dr. George Huston Bell was born in Mount Sidney, Va., on Aug. 10, 1866, one year after the close of the Civil War. He died suddenly in New York on Oct. 5, 1943. His father before him, Dr. William Bell, was a physician. He came of English and Scotch ancestry, long established in the Valley of Virginia. He received his early education at the Augusta Military Academy, Fort Defiance, Va., one of the best known preparatory schools for boys in the South. He obtained his degree of Doctor of Medicine from the University of Virginia in 1897. Immediately thereafter he entered on his long career in ophthalmology. In 1899 he completed his internship at the New York Eye and Ear Infirmary. His connection with this institution spanned a period of forty-five years, interrupted only once, in early life, by a year spent in postgraduate work in Europe. In 1917 he was appointed a full surgeon at the Infirmary, with a clinic of his own, Dr. Conrad Berens serving as his chief of clinic. Twelve years later, in 1929, he became consulting surgeon, which appointment he held until his death.

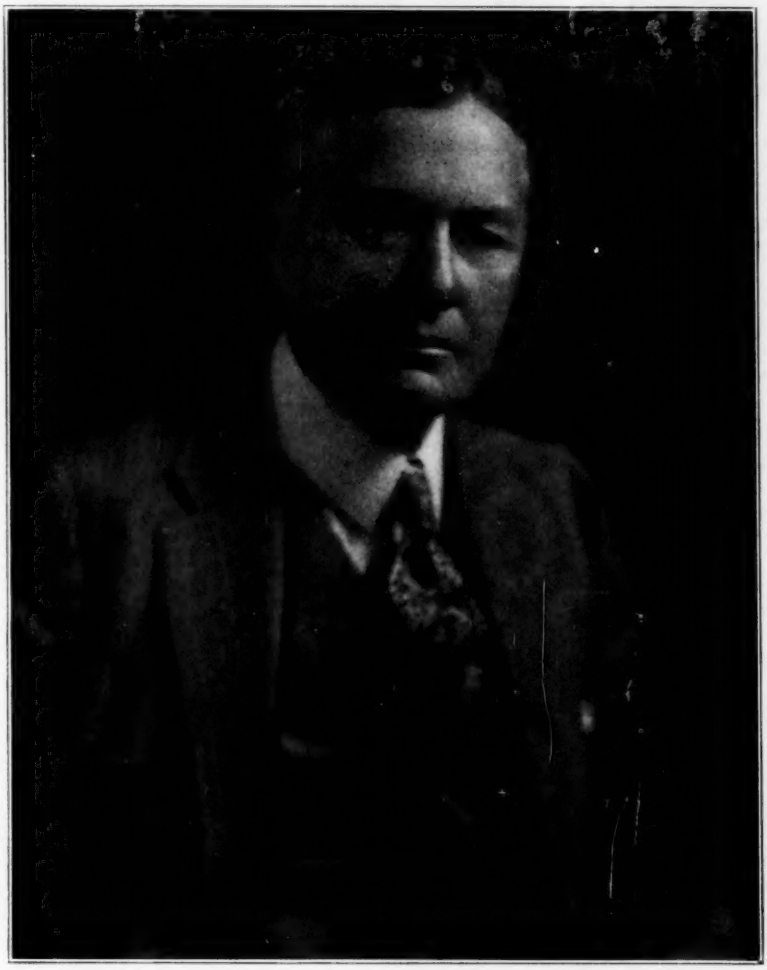
Although Dr. Bell's surgical activities were centered at the Infirmary, he found time to serve also on the staffs of other institutions, including the United States Marine Hospital on Staten Island, N. Y., the Hudson Street Hospital, the St. Andrew's Convalescent Hospital and the New York Polyclinic Medical School and Hospital, in which he was professor of ophthalmic surgery.

Most of Dr. Bell's contributions to the literature reflected the trend of thought of American ophthalmology in the early years of the present century. Thus, in his best known papers he discussed the teeth, the tonsils and toxemia, the "three T's" as he termed them, in their relation to diseases of the eye. He established the procedure against postoperative infection, now in use at the Infirmary, namely, the instillation of a 1 per cent solution of silver nitrate into the conjunctival sac an hour before the time set for operation. In a paper published in 1926 he was able to report on 1,500 major ophthalmic operations without a single infection. Toward the end of his surgical practice, when nearing the age of 70, he estimated that he had performed 3,000 cataract extractions.

He was a fellow of the American College of Surgeons, a member of the American Ophthalmological Society, a member of the New York Ophthalmological Society and a member of the New York Academy of Medicine.

Dr. Bell possessed a kindly, generous nature and retained to the last a high flow of spirits. He was an active member of the Virginia Society and the Southern Society in New York. In him the homing instinct was well developed. He maintained the old homestead, "Bellview Farm," near Mount Sidney, Va., where he passed his summer vacations. His clubs were the Ardsley Country Club and the Racket and Tennis Club. He belonged to the Phi Kappa Psi Fraternity. He was a Mason and a Presbyterian. In singular ways his life parallelel that of the late Dr. Robert G. Reese. They were born in the same year and were brought

up in the same county; their fathers had been surgeons in the Confederate Army; they attended the same schools; they both graduated in pharmacy before studying medicine; they belonged to the same fraternities; they interned at the same institution, and they both enjoyed a lucrative practice. No surgeons ever served the New York Eye and Ear Infirmary more faithfully and devotedly than these two men, and few over a longer period.



GEORGE HUSTON BELL, M.D.
1866-1943

Dr. Bell's death, at an advanced age, brought to an end a happy life, eminently successful in every way. He will be missed by many friends and patients. Surviving him are his widow, Mrs. Florence Winifred Collins Bell; a brother, Archibald H. Bell, of Richmond, Va., and three sisters, Mrs. Clifford Prater, of Knoxville, Tenn., Mrs. John Cyrus McCue, of Fort Defiance, Va., and Miss Willie Bell, of Mount Sidney, Va.

BERNARD SAMUELS.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Cornea and Sclera

TREATMENT OF EPIDEMIC KERATOCONJUNCTIVITIS. A. E. BRALEY and M. SANDERS, J. A. M. A. **121**: 999 (March 27) 1943.

The authors discuss 10 cases of epidemic conjunctivitis in which there were the following manifestations: pronounced edema of the lids, conjunctiva and semilunar fold, with bulbar chemosis; involvement of the preauricular lymph nodes, usually both the submental and the anterior cervical; severe ocular discomfort associated with excessive tearing; appearance in conjunctival scrapings of mononuclear cells with practically no polymorphonuclear leukocytes, and negative cultures.

In 9 of the cases striking clinical improvement occurred a short time after intravenous injections of human convalescent serum were given. However, need for a controlled group of cases cannot be stressed too strongly. It has been pointed out that there is no correlation between the intensity of the clinical symptoms and the duration of the disease. It should also be remembered that it is highly desirable that the present study be enlarged from the point of view both of cases in which there is treatment and of control cases, and that standard, accurately titered convalescent serums be employed.

W. ZENTMAYER.

ACNE ROSACEA KERATITIS AND RIBOFLAVINE (VITAMIN B_2). W. M. FISH, Brit. J. Ophth. **27**: 107 (March) 1943.

The author quotes from the literature to the effect that "rosacea keratitis (so-called) may be the direct result of deficiency of riboflavine" and further that "the term 'dietary keratitis' (used by Sydenstricker) appears to indicate a new designation of the condition familiar to ophthalmologists as rosacea keratitis, so-called." Fish considers this rather surprising in view of the fact that acne rosacea is a rare disease in the southern states of America, where riboflavin deficiency is common, and is not even mentioned in Sydenstricker's paper.

The author studied 45 patients with acne rosacea with the slit lamp in order to find out whether they showed the type of corneal vascularization demonstrated to him by Sydenstricker as diagnostic of ariboflavinosis, e. g., a bilateral, symmetric, superficial proliferation of new streamer-like fine vessels from the limbal loops, forming a more or less regular pattern all around the cornea and extending toward its center. Of these 45 patients all had the cutaneous and all but 2 the corneal lesions typical of rosacea, but only 3 had the bilateral corneal involvement, so that in 40 cases there was a control eye, unaffected by ulceration, in which to look for the corneal vascularization typical of ariboflavinosis, which, though not always equal in the two eyes, is always bilateral. This type of vascularization was absent in all 40 cases.

In the present series, rosacea keratitis does not appear to be the direct result of ariboflavinosis.

W. ZENTMAYER.

General

COLOUR IN PROTECTIVE NIGHT LIGHT. C. E. FERREE and G. RAND, Brit. J. Ophth. **27**: 173 (April) 1943.

Ferree and Rand state that in the selection of a color for protective night light, the ocular factors as well as power to penetrate the external atmosphere, should be taken into consideration—namely, the comparative sensitivity of the eye to colored light at very low intensities, visual acuity at low intensity and adaptation

factors. An instrument termed a variable illuminator has been made in the form of a lamp with the opening turned downward or obliquely downward. By means of a rotatable shutter the light can be varied in continuous change from full to extinction, so that it can be used as a night light to obtain a complete black-out or as near a complete black-out as may be desired. In this lamp any color, type or wattage of bulb can be used, even the small neon night bulb. Suitably equipped, it should serve a useful purpose in protection night lighting, even when total extinction of light for a complete black-out is necessary. W. ZENTMAYER.

Hygiene, Sociology, Education and History

OPHTHALMOLOGY AND SOCIOLOGY. A. LOEWENSTEIN, Bull. Czechoslovak M. A. in Great Britain, 1942, no. 3.

After discussing the main causes of blindness, the author suggests means of prevention. It is difficult to prevent hereditary disease or defects, and he suggests that advisory offices might be established where engaged couples could get guidance. Statistics have shown that blindness from venereal disease is rapidly decreasing. Antepartum treatment is now well established and is distinctly successful. The greatest modern problem is injuries in the industrial countries. Many injuries in workshops are due to defective illumination; the author states that at least 15 per cent of all injuries to the eyes are caused by insufficient lighting. In one factory, after modern lighting fixtures were installed, the frequency of accidents was reduced by 7 per cent. Also, industrial efficiency depends on good vision. It is necessary to control toxic materials, such as gases, dusts and vapors; to provide protective goggles against flying objects and radiant energy, and to provide adequate illumination. In the final section the author stresses the need of more careful teaching of ophthalmology in the medical schools. This would result in a great stock of good ophthalmic surgeons to carry on the battle for the sight of the rising generation. ARNOLD KNAPP.

Methods of Examination

NEUTRALIZING CYLINDER GLASSES AS TEST FOR MALINGERING. H. LYTTON, Brit. J. Ophth. **26:** 512 (Nov.) 1942.

Malingering by claiming a reduction in visual acuity to approximately the same extent in the two eyes is difficult to unmask.

Lytton has found the following test useful: In addition to the glass which gives the best possible correction, a plus cylinder glass, e. g., + 1.00 D. cyl., axis 90, is put in the rear immobile groove of the trial frame, and the corresponding minus glass, — 1.0 D. cyl., axis 45, is placed in the revolving compartment in front. Now the examinee is asked to change the axis of the minus cylinder by revolving it until he obtains the clearest definition of the test types. It speaks strongly for his honesty if he turns the axis into the neutralizing position of 90 degrees. A malingerer is likely to put the axis at 180 degrees. If he still claims to see, for instance, the fourth line of the chart, indicating a visual acuity of 6/18, it is proved that his vision is at least 6/9, as the crossed cylinder reduces the visual acuity about 50 per cent. W. ZENTMAYER.

Neurology

STUDIES ON THE CORPUS CALLOSUM: V. HOMONYMOUS DEFECTS FOR COLOR, OBJECT AND LETTER RECOGNITION (HOMONYMOUS HEMIAMBLYOPIA) BEFORE AND AFTER SECTION OF THE CORPUS CALLOSUM. A. J. AKELAITIS, Arch. Neurol. & Psychiat. **48:** 108 (July) 1942.

Three cases are reported in which routine perimetric fields were normal but homonymous hemiamblyopia was present. The methods of testing are described in detail. Briefly, the authors found gross studies more reliable and informative

than the use of small test objects on the Bjerrum screen. Such studies included appreciation of various shades of gray as utilized in Hering's gray paper series, appreciation of form by use of geometric figures as found in the Stanford-Binet series and attentiveness to two similar objects presented simultaneously to identical points in each homonymous field. Each patient showed loss of recognition of forms, objects and letters and impairment of attentiveness and of perception of illumination. The usual remark was, "I see something but don't know what it is."

Evidence in each of the cases suggested that the hemiamblyopia resulted from a lesion in the posterior portion of the contralateral hemisphere. However, the author points out that cases have been reported in which lesions of the optic tract were responsible, and he therefore concludes that hemiamblyopia has only limited localization value.

Complete or partial section of the corpus callosum produces no changes in the hemiamblyopic visual field.

R. IRVINE.

BOECK'S DISEASE (SARCOID) OF THE CENTRAL NERVOUS SYSTEM: REPORT OF A CASE, WITH COMPLETE CLINICAL AND PATHOLOGIC STUDY. T. C. ERICKSON, G. ODOM and K. STERN, Arch. Neurol. & Psychiat. **48:** 613 (Oct.) 1942.

A case is reported with complete clinical and pathologic study, showing a clinical picture of adhesive arachnoiditis with internal hydrocephalus. There was progressive bilateral papilledema with retinal hemorrhages and visual loss.

Biopsy of a nodular lesion from the upper lip established a diagnosis of Boeck's sarcoid, and examination of granulomatous processes within the central nervous system resulted in a similar diagnosis.

R. IRVINE.

HISTOGENESIS OF THE EARLY LESIONS OF MULTIPLE SCLEROSIS: I. SIGNIFICANCE OF VASCULAR CHANGES. M. SCHEINKER, Arch. Neurol. & Psychiat. **49:** 178 (Feb.) 1943.

The author provides the following summary:

"In 20 cases of multiple sclerosis the early stages of plaque formation and their relation to the vascular system were studied. A positive correlation was found between the early lesion and the presence of vascular abnormality. The view is expressed that vascular change, particularly occlusion by thrombosis, is an essential factor in the pathogenesis of demyelinated plaques."

R. IRVINE.

Ocular Muscles

ANOMALOUS RETINAL CORRESPONDENCE. D. E. DICKE, Am. J. Ophth. **25:** 585 (May) 1942.

Dicke reviews the frequency and manner of development of anomalous retinal correspondence and discusses the tests for its presence. She emphasizes the value of preoperative treatment of patients who will be subjected to surgical intervention.

W. S. REESE.

ORTHOPTIC TREATMENT OF ANOMALOUS PROJECTION. D. S. MANN, Brit. J. Ophth. **27:** 215 (May) 1943.

As indicated by the title of the article, Mann prefers Verhoeff's term—anomalous projection—of the many under which the phenomenon goes. Details of the preoperative treatment are given. Operation is almost inevitably necessary, and there is no point in prolonging treatment before operation if the patient shows no improvement after three or four visits. The only general prerequisites are that the vision should be equal and the patient should be able to alternate readily. When the

operative result is good, the probability is that some binocular vision may be recovered in time without orthoptic treatment. However, the recovery is seldom complete, and in general the postoperative treatment is essentially the same as the preoperative.

W. ZENTMAYER.

The Pupil

ANOMALOUS PUPIL REACTIONS. B. G. EDELSTON, Brit. J. Ophth. **26:** 507 (Nov.) 1942.

Three cases of anomalous pupillary reactions are reported. The first patient was a man aged 30 with tabes dorsalis. The pupils were small, equal and centrally placed. They dilated to an appreciable degree to light. There was early optic nerve atrophy. The Wassermann reaction was strongly positive. The second patient was a man aged 59. There was a history of a primary sore at the age of 29. The pupils were moderate in size, centrally placed and equal. Light stimulus caused a moderate dilatation. The Wassermann reaction was strongly positive. At autopsy a new pulmonary growth in a caseous condition was found. The third patient was a woman aged 28. The left pupil was larger than the right and was immobile to light but showed slight slow contraction in convergence. All the superficial reflexes except the biceps jerk were absent. The patient was normal in every other respect. Although when she was 10 years old a diagnosis of juvenile tabes was made, Edelston believes the pupillary phenomenon to be an example of myotonic pupil.

W. ZENTMAYER.

Refraction and Accommodation

MUSCLE BALANCE IN MYOPIA. W. W. BAUM, Am. J. Ophth. **25:** 291 (March) 1942.

In this rather brief article Baum concludes from his studies of muscle balance in myopia that orthoptic treatment is of definite value in the control of the common functional myopia seen in children and young adults.

W. S. REESE.

THE PROBLEM OF THE HYPERMETROPIC MINER. A. C. REID, Brit. J. Ophth. **27:** 110 (March) 1943.

Reid points out that the myopic miner who consistently wears his correction on top can dispense with glasses below ground. This is not true of the miner with high hypermetropia, who has to accommodate to see his work, since a miner's work is done mostly within arm's length. Fourteen cases of hyperopia of high degrees are recorded to show the points the author wishes to raise. Seven of the patients who had an error of between 2 and 4 in the lowest axis averaged 37 years of age, the extremes being 28 and 44. With a + 4 D. error few men can go beyond the age of 30 at the coal face. With an error of + 6 D. or more, probably no man should go below, and few do. It would therefore seem reasonable to advise lads with both eyes good not to go down if the error is + 3 D. or more and squinters or amblyopes not to go down at all. Much can be done in advising the parents when a boy is about to leave school.

W. ZENTMAYER.

Retina and Optic Nerve

NOTE ON SOME SYMPTOMS ASSOCIATED WITH A RETINAL LESION. E. G. HILL, Brit. J. Ophth. **27:** 97 (March) 1943.

At the age of 47 the author experienced some difficulty in vision accompanied by the appearance of a veiling patch of light. Corrected vision in each eye was 6/5. No scotoma was present. Ophthalmoscopic examination by Williamson-Noble disclosed in the right eye a shimmering area in the macular region which

the examiner attributed to some thickening of the internal limiting membrane of the retina. The fundus of the left eye was normal. The symptoms noted by the patient were image distortion with localized aniseikonia, the appearance of a luminous or a shadowy veil, a phenomenon termed the "after flash," convergence effect and pain. The author gives a detailed description of the symptoms and suggests the following explanation:

"The image distortion may presumably be attributed to a displacement of the retinal elements, and the character of the change shows that the centre of the retina must be bunched. The convergence effect seems to indicate a residual lack of rigidity in the posterior structure of the eye. It may also be mentioned here that, associated with these changes, a blind patch of ten minutes subtense made its appearance and is located, presumably significantly, exactly at the centre of the fovea.

"The flash and veil phenomena are presumably bound up with the bleaching of the visual purple, and it would seem that the lesion has disturbed this mechanism over the affected area. As there is no reduction in the level of dark adaptation, the failure seems more related to the actual bleaching reaction than to the secretion of visual purple. The discrimination between the effects in blue and other colours may contribute to the elucidation of the mechanism of dark adaptation, as there is reason to suppose that the rate of dark adaptation is a function of the colour of the preadapting light."

The article is illustrated.

W. ZENTMAYER.

ON SOME ANOMALOUS FORMS OF AMAUROTIC IDIOCY AND THEIR BEARING ON THE RELATIONSHIP OF THE VARIOUS TYPES. R. WYBURN-MASON, Brit. J. Ophth. **27:** 145 (April); 193 (May) 1943.

Wyburn-Mason reports a group of cases of amaurotic idiocy of the type described by Tay, in some of which there were atypical features. This is followed by a group of cases of the juvenile type; in some of these the disease was of the late infantile type described by Bielschowsky under the term "late infantile familial amaurotic idiocy with cerebellar symptoms." Still another group comprises instances of the late juvenile type. Finally, an adult type is described.

Evidence is brought forward that there are two types of the disease, infantile and juvenile, which are not related to one another except in their similar histologic appearances. It is probable that atypical forms of the juvenile disease occur in which either the retinal or the cerebral manifestations are absent, especially in older patients. It seems likely that the disease is unrelated to macular heredodegeneration.

The article is illustrated with fundus drawings.

W. ZENTMAYER.

Trachoma

SULFANILAMIDE IN THE TREATMENT OF TRACHOMA. R. SORY, Am. J. Ophth. **25:** 713 (June) 1942.

Sory presents the following summary and conclusions:

"1. In experiments for control, patients receiving sulfanilamide by mouth underwent treatment in one eye with drops of the drug, and in the other with either grattage or application of silver or copper salts; recovery from infection occurred only in the latter eye.

"2. Of 49 patients treated with sulfanilamide alone, the condition in 14 was unchanged, in 21 improved, and in 14 arrested, 7 of the cases being of the "flare-up" variety.

"3. The drug had least beneficial effect on papillary or follicular hypertrophy of the conjunctiva; its best effect was on the corneal lesion associated with the "flare-up" type.

"4. In combined sulfanilamide and other treatment, an analysis of 274 patients reveals arrest in 235 (86 per cent), improvement in 38 (14 per cent), and no change in one.

"5. In the combined therapy, grattage and chemical treatment were of approximately equal effectiveness; their selection should vary in different patients depending upon the character of the disease.

"6. In operations performed to correct sequelas of trachoma, it is thought that sulfanilamide may also be of use.

"7. The results of this study indicate (*a*) that sulfanilamide only exceptionally arrests trachoma, and by itself is less reliable than other accepted forms of treatment; (*b*) in conjunction with other therapeutic measures, recovery is accelerated, and a high degree of efficacy is readily attainable; (*c*) even in the latter instances recurrences may occur, suggesting that trachoma is, as formerly, *arrested* and not *cured.*"

W. S. Reese.

Uvea

Progressive Atrophy of the Iris with Formation of Holes and Increased Intraocular Tension: Report of Cases. J. Scharf, Klin. Monatsbl. f. Augenh. **106:** 411 (April) 1941.

Two cases of progressive atrophy of the iris with formation of holes in the iris and increased intraocular tension are reported. The patients, both women, were 51 and 26. The result of gonioscopic examination is described and evaluated. As this disease is described by a number of writers quoted, great rarefaction of the stroma of the iris occurs with progressing formation of holes, the area of the sphincter remains intact the longest and glaucoma of a malignant type follows, resisting all local and surgical therapy. Usually only one eye is affected. Regarding the origin of glaucoma, no agreement was arrived at by a number of observers. Scharf found peripheral synechias causing adhesions between the root of the iris and the inner corneal surface at a time when no evidence of glaucoma could be obtained, not even by provoking tests. Furthermore, he does not accept the theory that accumulation of pigment and obliteration of the canal of Schlemm may be the cause of glaucoma, because considerable pigmentation of this area was observed in his second case in the absence of glaucoma.

In the author's opinion the disease described is due to developmental disturbances of the mesoderm of the anterior segment of the eyeball. The uveal fetal tissue, which is only sparingly preserved at birth, still exists in the form of peripheral synechias. When it completely disappears it pulls the peripheral portion of the iris toward the root of the iris. Thus the iris, being increasingly stretched between the peripheral adhesions and the forming ectodermal sphincter, will suffer progressing atrophy, followed by formation of holes.

K. L. Stoll.

Therapeutics

Vitamin Therapy in Ophthalmology. A. M. Yudkin, Am. J. Ophth. **25:** 284 (March) 1942.

Yudkin concludes as follows:

"Throughout the discussion, no mention was made of any specific form of vitamin and I avoided speaking about the recent miraculous cures of ocular disturbances by factors of the vitamin-B group. These results have not been repeated by enough clinicians to warrant their general use in ophthalmic practice. The vitamin-B group may be obtained in concentrated form if the patient objects to brewer's-yeast powder. The fish-oil concentrates may be substituted for cod- or halibut-liver oils. There is, however, no substitute for a well-balanced diet."

W. S. Reese.

Society Transactions

EDITED BY DR. W. L. BENEDICT

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

DANIEL B. KIRBY, M.D., *Chairman*

R. TOWNLEY PATON, M.D., *Secretary*

Jan. 18, 1943

Military Ophthalmology. DR. W. THORNWALL DAVIS (by invitation).

Injuries to the eye in war are of the same type as those in civilian life but are likely to be more severe. The conditions under which such wounds and injuries are received and treated render them more dangerous. The extremely rapid movments of troops and weapons, the much greater firing power and the aerial bombing, with tremendous explosive force, all make difficult or impossible the adequate care of wounds of all sorts, those of the eye included. Hence, although injuries to the eye in wartime are akin to those in peacetime, the facilities for their care are entirely different. It is from this point of view that observations should be made. For persons who have not had military service this is difficult.

Thermal burns constitute the great majority of all injuries to the eyes in the present war, far exceeding those in any previous one. So far, many more foreign bodies are found in the globe in this war than in World War I. Most of them are nonmagnetic.

The methods of treatment in the field of all the unspeakably horrible injuries to the eyes were discussed. Treatment at the front is medical first aid, and on its proper administration will depend the saving or loss of many eyes. Surgical treatment in hospitals for such eyes is not discussed, since this is not a military problem and differs in no way from the treatment in civilian life.

The importance of a proper understanding of color vision, night vision, anoxia and high altitude flying is discussed. Most of this knowledge is relatively new, and some of it is not yet available to members of the medical profession.

The great importance of aviation medicine, particularly the part related to ophthalmology, was emphasized.

Penicillin and Sulfadiazine in Treatment of Experimental Intraocular Infection with Pneumococcus. DR. LUDWIG VON SALLMANN.

This paper was published in full in the October 1943 issue of the ARCHIVES, page 426.

DISCUSSION

DR. DANIEL B. KIRBY: I am interested to know how penicillin came to be employed. Can Dr. Meyer say something about the chemistry of this product and the nature of its action?

DR. KARL MEYER (by invitation): Perhaps I should say a few words, not so much about the chemical composition of penicillin, which is complicated and to a large extent still unknown, as about some bactericidal or bacteriostatic products of bacterial origin which have been under investigation in the last few years. Such substances have been obtained from bacteria and from molds and fungi.

The most widely known and the most thoroughly studied so far is gramicidin, which was discovered and investigated chiefly by Dubos and his collaborators at

the Rockefeller Institute for Medical Research. Gramicidin is a polypeptide of large molecular weight, derived from Bacillus brevis. It has been used locally only, since it is hemolytic and highly toxic when given systemically. It has been used in surface wounds, such as ulcus cruris, with excellent results. However, as my associates and I at the Institute have convinced ourselves, it is inhibited by naturally occurring substances and therefore has a limited application. Dr. Thygeson used it in a few cases of blepharitis, with discouraging results.

Other agents of bacterial origin have not been studied clinically to any extent. Most of them offer no hope because they are highly toxic, even in minute concentration, or their potency is too low.

However, penicillin, which is a yellow pigment derived from Penicillium notatum, has been administered to a fairly large number of patients by intravenous, subcutaneous or intramuscular injection. This work of Dr. von Sallmann's is the first in which the drug has been introduced into a body cavity by iontophoresis. Penicillin is suited for chemotherapeutic work because it is not influenced by body constituents and, further, is relatively atoxic; 1 Gm. per kilogram of mouse is the minimal lethal dose. Less than 1 mg. of penicillin has been found effective in cure of an infection with about 1,000,000 times the fatal dose of streptococci. In vitro the effect is still more remarkable, in that 0.00001 mg. is enough to kill between 2,000,000 and 3,000,000 virulent hemolytic streptococci. In this country, effective cures have been reported in cases of pneumococcic meningitis, staphylococcic meningitis, sepsis due to the streptococcus, staphylococcus and pneumococcus and osteomyelitis. In most of these cases previous treatment with a sulfonamide compound was unsuccessful, either because the drug was not effective or because the patient did not tolerate it.

The disadvantages of treatment with penicillin are as follows: first, there is the high cost of the product. The molds from which it is produced must be grown in rather large quantities, and the procedures of extraction and purification are expensive. However, the greatest disadvantage of the treatment is the instability of the compound. Preparations of penicillin, at least in the form of the free acid, have to be sealed in high vacuum, since they are unstable in powder form under ordinary conditions. Aqueous solutions are very unstable, and, in our experience, more than half the activity is lost after twenty-four hours at room temperature. The third disadvantage is the rapid excretion of penicillin through the kidney, so that injections have to be given at intervals of three to four hours. Chemically, penicillin is a rather strong acid, which forms water-soluble salts. This property explains, in part at least, the low toxicity and the rapid excretion. However, now there is good reason to think that the latter problem is solved, as new derivatives of penicillin have been prepared which are not water soluble and which are slowly hydrolyzed by the body enzymes.

Perhaps I should say a few words about the availability of penicillin, or, rather, its nonavailability at present. Certainly, less than 200 patients have been treated in the United States in a period of one and a half to two years. The commercial manufacture of penicillin is under government control, and only a limited amount of the substance is available, and then to a few selected clinics. It is imperative that the structure of penicillin be determined and that it be synthesized in the laboratory, and I believe this can be done. There is no question that penicillin is one of the most promising chemotherapeutic agents.

DR. DANIEL B. KIRBY: Certainly, one should not permit an agent like penicillin to be dropped without making every effort to establish its use. I believe Dr. Knapp had the opportunity to watch this experiment as it was carried out; perhaps he would like to comment.

DR. ARNOLD KNAPP: I am sorry that I cannot discuss Dr. von Sallmann's admirable presentation from the scientific point of view. I remember, however, that he told me that injuries to the cornea had occurred in some of his experiments; as this is of practical importance, I should like to ask Dr. von Sallmann to explain it.

DR. LUDWIG VON SALLMANN: I wish to thank Dr. Meyer for the valuable information presented in his discussion. Although hope of the availability of penicillin for general clinical use in the near future seems slight, ophthalmologists are in a somewhat better position, since only about a hundredth of the average dose for a systemic infection is sufficient for the complete course of treatment of an ocular infection.

With regard to Dr. Knapp's question concerning corneal damage through treatment with penicillin, it can be stated that in rabbits repeated corneal baths with a 0.25 per cent solution in five minute applications did not cause damage. Neither did the iontophoretic introduction of a 0.1 per cent solution. However, repeated iontophoretic applications of a 0.25 per cent solution produced large erosions, which usually healed in several days without residual opacity of the cornea. A 0.25 per cent solution, self instilled, did not cause any burning or discomfort. One patient treated repeatedly with corneal baths and hourly instillations of a 0.25 per cent solution did not show any harmful effect.

Topography of the Orbit with Particular Reference to Retrobulbar Injection.
DR. ROBERT LAMBERT and DR. VIRGINIA LUBKIN (by invitation).

An anatomic study of the retrobulbar space is reported, with several cross sections of normal specimens. Fluids were injected into this space post mortem, with removal and section of the entire orbital contents. Injections of 4 per cent procaine hydrochloride were made in vivo. Of several approaches to the muscle cone, the preferred one is the inferior temporal. The quantity of fluid which most reliably produces analgesia of the cornea and bulb and nearly complete immobility of the globe is 3.5 cc. The first sign that the needle is in the muscle cone is dilatation of the pupil. The full effect of the injection occurs in fifteen minutes, and some anesthesia lasts about an hour. The pathways taken by the injected fluid are carefully mapped. The solutions diffuse without difficulty between the muscles to the spaces outside the cone and thence forward to the lids. They also enter the episcleral space through gaps in Tenon's capsule around the entrance of the optic nerve, and may flow forward to produce chemosis. This pathway was confirmed by the observation that the globe was stained posteriorly in numerous cases of enucleation in which the procaine given by retrobulbar injection was colored with methylene blue (methylthionine chloride). A number of interesting physiologic effects, such as anesthesia of the optic nerve, paralysis of accommodation and changes in tension, are noted. The lack of necessity of anesthetization of the ciliary ganglion itself is commented on.

DISCUSSION

DR. ROBERT LAMBERT: In discussing this work I should like to submit a few sections and mention some practical points.

The first section is intended to demonstrate what one does not see in the ordinary sagittal section of the orbit, namely, an optic nerve nicely shown. Because of the torsion of the vessels and the nerves, one rarely gets a continuous view of any structure. Therefore sagittal sections were discarded and cross sections utilized. In the second slide, at the apex of the orbit, one encounters the main branches of the ophthalmic artery, which is in one of its turnings, and one sees it laterally on section. The close proximity of the four muscles is shown, with their entering nerves and structures. The thickness of the vaginal sheath is to be noted, because under ordinary circumstances it protects the optic nerve from procaine or other medicaments injected.

Proceeding forward to about 1 cm. in front of the orbital apex, one can see the cells of the ciliary ganglion, which is situated between the nerve and the external rectus muscle. Still farther forward, as the muscle cone widens out, one sees the nerve posterior to the point where the central retinal artery and vein pierce the sheath. The next slide shows the point where the central

retinal vein is about to leave the nerve. The reason that anesthetization of the ciliary ganglion is not vitally important is evident, since most of the structures leading to the globe are more exposed to injected substances just posterior to the globe. In another slide, taken just behind the globe, the central retinal artery and vein are present. The vein is collapsed.

One can even elevate the tension in the eye by a small injection of fluid, which is sufficient to compress the thin-walled veins and yet not sufficient to compress the heavy arteries.

The following practical points may be stressed: First, "ciliary ganglion block" should be discarded, and "muscle cone injection," as suggested by Dr. Walter Atkinson, Dr. Rudolf Aebli and others, should be substituted. We suggest that the control over tension prior to operation for glaucoma and other surgical procedures is chiefly accomplished by the use of epinephrine in the injected fluid. In the face of some contradictory evidence from other workers, I cannot positively state that the tension cannot be lowered with procaine alone, although we never succeeded in doing so. Only the injections in which epinephrine was added to the solution of procaine really lowered the tension appreciably. Control of the tension can be modified by the amount of epinephrine in the fluid injected. In my opinion, the time of injection has not been sufficiently emphasized. In preoperative injections into the muscle cone most of the effects of the injection take place when the patient is back in his room. If one makes the injection prior to scrubbing, or about fifteen or twenty minutes before operation, one obtains the full effect, including the loss of muscle power and complete paralysis of the eye. One obtains almost complete ptosis, and the eye is stationary during the operation. This, in my opinion, is a surgical advantage. Lastly, I submit that by a direct approach to the circulation in this manner more possibilities for the investigation and treatment of disease, particularly glaucoma, are afforded.

DR. ARNOLD KNAPP: Dr. Lambert said that one is apt not to wait long enough before the operation to obtain complete anesthesia from a retrobulbar injection. Such a delay, in my experience, leads to softening of the eyeball, which is not desirable, unless in the presence of glaucoma, and makes the selection of the proper interval difficult.

DR. RUDOLF AEBLI: Injection into the muscle cone was introduced by Dr. Knapp in 1884. Dr. Atkinson has reviewed the subject in his paper on local anesthesia in ophthalmology (*Tr. Am. Ophth. Soc.* **32**: 399, 1934). In cases of extraction of cataract I like to make the injection just before I am ready to proceed with the section. If one waits ten or fifteen minutes after making the injection, the low tension frequently increases the difficulty of extraction.

What is the cause of the hypotony? Is it due to constriction of the vessels or to paralysis of the sensory nerve, which may in some manner influence the secretion of the aqueous from the columnar cells in the ciliary body?

DR. DANIEL B. KIRBY: I should like to have Dr. Lambert state how many experiments were done on the living subject, and what were the indications for the experiments, if there was no particular reason for ophthalmic treatment, and how many of the specimens were obtained from the cadaver.

DR. ROBERT LAMBERT: Sixty experiments were done on the cadaver in order to determine exactly where the substance was introduced, and 65 experiments were done on the living subject. The essential purpose of the experiments was to study the influence of the injections on tension, but such variations were obtained with different sites of injection and different quantities of fluid that the need first of an accurate topographic technic is apparent.

In reply to Dr. Knapp's statement, hypotony depends not only on the time of injection but on the amount of epinephrine in the injected fluid, the two most important variables I know of at present.

Bilateral Uveitis, Poliosis and Retinal Detachment with Recovery: Report of a Case. DR. ISADORE GIVNER.

This paper was published in full in the September 1943 issue of the ARCHIVES, page 331.

DISCUSSION

DR. LUDWIG VON SALLMANN (by invitation): Dr. Givner's case of bilateral uveitis and poliosis, complicated by partial detachment of the retina and secondary glaucoma, has received an extremely thorough study. The many methods applied indicate his thoughtful approach to the diagnostic problem, and they are to me most instructive and stimulating, since they demonstrate the various possibilities that must be kept in mind in an attempt to establish the etiologic diagnosis. Although most of these tests gave negative results, they serve as a reminder that such investigations should be made under similar conditions. In suitable cases other parts of the eye may be examined, and mouse brain studies may be indicated.

The second point of interest in Dr. Givner's case concerns the classification. In my opinion, it is not worth one's effort to argue on the closeness of the relation of such a borderline condition to Harada's disease or to the so-called Vogt-Koyanagi syndrome, since the etiologic factors and the specific treatment are not determined, but a disorder characterized by bilateral uveitis, scleritis and localized detachment of the retina, without meningeal symptoms, should not be diagnosed as Harada's disease, as has been done repeatedly in the literature. It would be interesting to hear Dr. Givner's opinion on this point of classification.

DR. ANDREW RADOS, Newark, N. J.: Harada's disease, described first in 1926, is an interesting and distinct entity. Clinically, the disorder has specific pathologic changes. It is always bilateral, never unilateral, in contradistinction to the conditions associated with scleritis and other diseases resulting in inflammatory detachment of the retina, in which it is always unilateral. Harada's disease is closely related to the Vogt-Koyanagi syndrome; in both instances the condition is always bilateral and is accompanied by systemic changes. Furthermore, the clinical picture is characteristically so severe that recovery in the majority of cases is all the more surprising.

Furthermore, the specificity of the ophthalmoscopic picture after the uveitis has cleared is of interest. Proliferation of pigment and depigmentation is not so conspicuous in any other type of uveitis.

The etiologic factors are not known. Whether Harada's disease is a variety of the Vogt-Koyanagi syndrome has not been settled. The literature tends toward a dualistic point of view. In cases of Vogt-Koyanagi disease the uveitis itself is always more serious in the anterior segment of the eye; in cases of Harada's disease the anterior segment of the eye is usually free of symptoms, or they are slight. There are cases of Harada's disease in which no lesions of the anterior segment or only few keratotic deposits are apparent in the beginning. In cases of Harada's disease poliosis and alopecia may be present, but are rare, whereas in cases of Vogt-Koyanagi syndrome bilateral uveitis, poliosis and alopecia exist, and vitiligo and dysacousia may be present, but not in all instances. With the Vogt-Koyanagi syndrome, the aforementioned changes in the integument and hair not only are present but are usually bilateral; on the other hand, with Harada's disease they are usually missing, but uveitis, with the simultaneous detachment of the retina in both eyes, is present.

The histologic changes are not well known. I should like to show two slides. One is from a case of Vogt-Koyanagi disease in which enucleation was finally done; in the upper part of the slide the normal retina and the tremendous infiltration of the choroid appear. In only two other conditions is the degree of choroidal infiltration of equal severity—one is sympathetic ophthalmia and the other leukemia. In the majority of sections the infiltration consists almost solely of plasma

cells. Choroiditis with infiltration of plasma cells may indicate only the presence of an acute inflammation and is not necessarily a specific type of choroiditis, although choroiditis with the cellular elements entirely of the plasma cell type is never seen.

The high magnification in the second slide shows well the individual plasma cells forming the infiltration. If it is considered that the Vogt-Koyanagi syndrome and Harada's disease belong to the same group as sympathetic ophthalmia, as is repeatedly stated in the literature, no point of similarity except the severity of the inflammation is apparent. Sympathetic ophthalmia is one of the most severe forms of uveal inflammation. Dr. von Sallmann hesitated to classify Harada's disease as a separate entity because of lack of knowledge of its cause and treatment. The cause of sympathetic ophthalmia is not established either; nevertheless, it has been differentiated as a disease entity.

The cause of Harada's disease is unknown. Tuberculosis and virus infection have been suggested. There is only 1 case in which consanguinity was mentioned, that of Zentmayer. That a disease of such severity, and one in which bilateral detachment of the retina has occurred, should ever be cured spontaneously is unusual and is contrary to what happens in other types of uveitis.

Book Reviews

Reconstructive Surgery of the Eyelids. By Wendell L. Hughes. Price, $4. Pp. 160, with 198 illustrations. St. Louis: The C. V. Mosby Company, 1943.

In this monograph the author presents a comprehensive review of the historical background of plastic surgery of the eyelids. The first chapter, which is devoted to the early development of skin grafting, contains much valuable information and gives the reader a clear conception of the progressive steps through which the reconstructive surgery of the eyelids has passed.

The problem of grafting without a pedicle is then considered in a similar manner, with an interesting résumé of the literature. Two case reports are given to illustrate the technic advocated by Wheeler of the use of a full thickness graft from one eyelid to another. The variations in types of pedicle grafts are discussed, as is the use of split skin grafts. A brief description of the sources of skin used for grafting is included in the chapter devoted to the operative technic, in which the author correctly emphasizes the importance of attention to such details as preparation of the skin to be grafted and pressure dressings.

The technic of the use of buccal mucous membrane to replace the conjunctival layer is given, as are some of the older methods of reconstruction of the tarsus. The author then reports in detail his method of reconstruction of the lower lid. In this operation the upper lid is split, and its tarsus and conjunctiva are used to line the new-formed lower lid, the skin layer of which is formed by undermining of the skin of the cheek. Several illustrative case reports with photographs demonstrate the efficiency of this technic. The freedom from additional scars, together with the normal function and excellent appearance of the newly created lid, makes this the method of choice when total reconstruction of the lower lid is necessary.

This volume is replete with illustrations, many of which are excellent, while others are poor. The case reports scattered throughout the book add little to its value. The complete bibliography, with its list of 451 references covering all phases of the subject, greatly increases the worth of the book.

It is to be recommended to all ophthalmologists, and particularly to those interested in plastic surgery.

J. H. DUNNINGTON.

The Extra-Ocular Muscles: An Outline. By Wendell L. Hughes, M.D. Second edition. Paper. Price $2. Pp. 32. New York: Printed privately, 1939.

This short pamphlet, being in outline form, is not easy reading; yet it contains an amazing amount of factual material, which probably cannot be found in any current textbook. Only one serious omission is noted. Under "Orthoptic Training," exercises for development of fusion in cases of alternating and monocular strabismus are given in considerable detail, without any mention of abnormal retinal correspondence. Apparently, the author was unaware of the disastrous results that are almost inevitable when exercises are undertaken without due consideration of the retinal correspondence. Such an omission is regrettable in a work that is otherwise sound.

Possibly the author believed that the cover test for diagnosis of a muscle anomaly has been so widely accepted that it needed only to be named. Unfortunately, this is not true, and by describing other tests in detail he has failed to give the cover test its proper emphasis. To find tenotomy of a rectus muscle given as an operation of choice or even as a possibility, is an unpleasant surprise. With these few exceptions, this outline is, in my opinion, the best available survey of the better present day teachings concerning the extraocular muscles. Because

of its brevity and its disconnected form, the work does not fill the great need of the beginner, but it should serve as a valuable reference and as an excellent review of the subject.

Persons who wish to secure the pamphlet may apply to Mrs. Stewart, 218 Second Avenue, New York Eye & Ear Infirmary, New York.

MAYNARD WHEELER.

Vertebrate Photoreceptors. By Samuel R. Detwiler. One of a series of Experimental Biology Monographs. Cloth. Price, $4. Pp. 184, with index and 110 figures. New York: The Macmillan Company, 1943.

From time to time a book appears that contains precise technical information, presented so simply, clearly and interestingly that it makes good reading for professional and lay student alike. Such is this latest publication in the series of "Experimental Biological Monographs." Although some attention is paid to the retina as a whole, it is the visual cells and retinal pigment that receive major attention.

After a preliminary chapter on the vertebrate eye as a unit, the organization of the retina is described; here the reader may obtain a digest of the far reaching and revolutionary concept of Polyak concerning the types of neurons encountered in the primate retina, their synaptic relations and the paths taken by retinal impulses. Succeeding chapters deal adequately with the development of retinal elements and the structure of visual cells and contain a discussion of the basis for identification of rods and cones in their more aberrant forms.

From this point on, the treatment shifts from purely morphologic considerations to a discussion of functional correlations and interpretations. In rapid sequence are presented the correlations between retinal structure and animal habits; the nature and degree of the positional changes through which the rods, cones and pigment of some vertebrates respond to such stimulating agents as light and temperature, and the significance of photomechanical changes, especially in regard to the duplicity theory.

The later chapters doubtless hold the greatest interest and value to the ophthalmologist. Two chapters are devoted to the arrangements by which visual acuity is attained, especially the significance of the fovea. The correlation between foveal development and the ability to perform extensive ocular movements is accepted, but the author concludes that conjugate movements, binocular vision and partial decussation of the optic tracts are not necessarily implied. He also demurs against Elliot Smith's view that the presence of a macula has led to important evolutionary advances in the portions of the brain concerned with vision. Walls's recent interpretation of the fovea as a mechanism for enhancing the resolving power of the retina, not for mere optical thinness and homogeneity, is given sympathetic consideration. This theory of Walls is one that cannot be ignored by any serious student who is concerned with the eye as an optical instrument.

Two final chapters center about the retinal photopigments. The background is painted through an exposition of the properties of rhodopsin and the less familiar porphyropsin of the rod and iodopsin of the cone. The relations of these carotenoid derivatives to the A vitamins (as both precursor substances and decomposition products) are reviewed on the basis of Wald's recent, important disclosures. The author identifies the Kolmer droplets, seen abundantly alongside dark-adapted rods, as retinene—the decomposition product intermediate between vitamin A and visual purple. In conclusion, there is a timely digest of the dependence of vision on vitamin A, of the effect of its deficiency on physiologic thresholds (night blindness), of the breakdown of rods following prolonged avitaminosis A and of the capacity of the rods for repair after a return to an adequate diet.

This monograph carries 110 excellent illustrations, several extensive tables, a recapitulation, a valuable bibliography, against which textual statements may

be checked, and both an adequate author and an adequate subject index. It contains some original data, of use as source material to the specialist. Ophthalmologists and all others interested in the retina are placed in heavy debt to Professor Detwiler for having produced a stimulating and authoritative book in a field that has been both enlarged and quickened through his own investigative activities.

L. B. AREY.

Rehabilitation of the War Injured: A Symposium. Edited by William Brown Doherty, M.D., and Dagobert D. Runes, Ph.D. Price, $10. Pp. 684. New York: New York Philosophical Library, Inc., 1943.

This volume is comprised of a series of articles by some fifty authors dealing with various phases of rehabilitation of those injured in the war. The material is divided into seven sections: viz., neurology and psychiatry; reconstructive and plastic surgery; orthopedics; physical therapy; occupational therapy and vocational guidance; legal aspects of rehabilitation, and miscellaneous subjects.

In the section devoted to plastic and reconstructive surgery the articles of greatest ophthalmologic interest include a description by Wendell L. Hughes of his ingenious method of rebuilding the lower lid and a short discussion by Dr. William B. Doherty on orbital implants. Both these papers were previously published in the ARCHIVES and are well known to most ophthalmologists. The Hughes operation has stood the test of time and can be recommended. The use of vitallium spheres for orbital implantation, as suggested by Doherty, is also worthy of further trial. "Practical Uses of the Tubed Pedicle Flap" is ably discussed by Sir Harold Gillies in an article replete with illustrations and concluding with a table of "conditions in which a tubed flap is preferable to a free graft." Several other papers included in this section should prove interesting and of value to ophthalmologists doing plastic surgery. The other articles dealing with ophthalmologic subjects are found in the section on occupational therapy and vocational guidance. R. C. Davenport outlines the rehabilitation of patients with nonrecoverable injuries of the eye and stresses the advisability of early treatment and individual care. Lady Duke-Elder considers the rehabilitation of patients with recoverable injuries of the eye, placing proper emphasis on the need for rapid restoration of physical fitness and the use of exercises well within the limits of the visual capacity of the patient.

This book, with its many authors, necessarily lacks continuity of style; nevertheless it contains many helpful suggestions to those interested in rehabilitation of the war injured. Some of the articles and illustrations are poor, others are very good. It is this lack of uniformity that detracts from an otherwise excellent symposium.

JOHN H. DUNNINGTON.